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VOLUME 12

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[1] J. B. Austin and R. H. H. Pierce, *J. Amer. Chem. Soc.* **55**, 661 (1933).

[2] J. R. Goldsmith, D. L. Graft and O. I. Joensuu, *Geochim. et Cosmochim. Acta* **7**, 221 (1955).

[3] S. T. Yoffe and A. N. Nesmeyanov, *Handbook of Magnesium-Organic Compounds* Vol. II, p. 239. Pergamon Press, London (1956).

Abbreviations are used freely in *Tetrahedron*, particularly in setting the experimental section. For the most part these are not followed by a full stop (period). Among the more commonly used abbreviations, these may be listed:

g kg mm cm ml cc cm^3 sec min hr n_D^{25} $[\alpha]_D^{25}$ 25° (without C which is always understood) but m.p., b.p., l. (litre), in. (inch) but in^2.

New compounds should be indicated by underlining the name (for italics) at its first mention (including headings) in the experimental section only, and by giving analytical results in the form: (Found: C, 62·9; H, 5·4. $C_{12}H_{12}O_4N$ requires: C, 63·2; H 5·3%).

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VOL.
12
1961

LIST OF CONTENTS

VOLUME 12

NUMBERS 1/2

L. PICHAT, M. HERBERT et M. THIERS: Etudes sur les méthodes de préparation de la sélénocystamine, sélénohypotaurine et sélénotaurine 1
G. KRESZE und G. SCHULZ: Additionsreaktionen der Nitrosogruppe—II. Diels–Alder-Reaktion mit cyclischen Dienen; Synthese einiger *cis*-4-Phenyl-aminocyclanole 7
P. YATES and P. EATON: The rearrangement of 4,5,6,7-tetrachloro-3a,4,7,7a-tetrahydro-4,7-methanoiden-8-one 13
Z. KECKI: The role of acidity in the kinetics of aromatic compound nitration 23
B. D. PEARSON: The electronic spectra of the nitronaphthylamines . . 32
A. J. BOULTON and A. R. KATRITZKY: The tautomerism of heteroaromatic compounds with five-membered rings—I. 5-Hydroxyisoxazoles–isoxazol-5-ones 41
A. J. BOULTON and A. R. KATRITZKY: The tautomerism of heteroaromatic compounds with five-membered rings—II. 3-,4- and 5-amino- and acetamido-isoxazoles 51
B. MAJHOFER-OREŠČANIN and M. PROŠTENIK: Studies in the sphingolipids series—XVII. Synthesis and resolution of erythro and threo-C_{02}-dihydro sphingosines. 56
N. K. KOCHETKOV, L. J. KUDRYASHOV and B. P. GOTTICH: Ketovinylation of β-dicarbonyl compound 63
M. I. KABACHNIK, S. T. IOFFE, E. M. POPOV and K. V. VATSURO: *Trans*-enolization 76
D. N. KIRK and V. PETROW: The stereochemistry of some halogenocholestan-3-ones 95
T. R. GOVINDACHARI, B. R. PAI, K. K. PURUSHOTHAMAN and S. RAJADURAI: Structure and stereochemistry of jatamansone 105
Errata:
B. A. PORAI-KOSHITS: The structure of aromatic diazo-compounds . . 113
P. MADHAVAN NAIR, R. SRINIVASAN and K. VENKATARAMAN: Condensation of 2,4-dinitrochlorobenzene with *o*- hydroxyarylamides 113
A list of some of the papers to be published in future issues 114

NUMBER 3

HERBERT C. BROWN: Hydroboration—A powerful synthetic tool . . . 117
G. W. K. CAVILL, P. S. CLEZY and F. B. WHITFIELD: The chemistry of mould metabolites—IV. Reductive acetylation and reoxidation of some phenoxazin-3-ones 139
A. JULG: Théorie du pouvoir rotatoire naturel. Dans la méthode des orbitales moléculaires 146
J. W. POWELL and M. C. WHITING: The analysis of mixtures of octalins . 163
J. W. POWELL and M. C. WHITING: The decomposition of sulphonylhydrazone salts: mechanism and stereochemistry—II. The pyrolysis of the diazodecalins 168
K. AGHORAMURTHY, K. G. SARMA and T. R. SESHADRI: Chemical investigation of Indian lichens—XXIV. The chemical components of *Alectoria virens* Tayl. Constitution of a new depsidone, virensic acid 173

G. H. KULKARNI, A. PAUL, A. SOMASEKAR RAO, G. R. KELKAR and S. C. BHATTACHARYYA: Terpenoids—XXIV. Isolation of 12-methoxydihydrocostunolide from costus root oil 178
PING-YUAN YEH and PIH-KUEI HUANG: Malvidin 3-galactoside and delphinidin 7-galactoside from *Baldhia sieboldhi* 181
W. G. DAUBEN and R. L. CARGILL: Photochemical transformations—VI. Isomerization of cycloheptadiene and cycloheptatriene 186
Book Reviews:
R. M. ACHESON: "An Introduction to the Chemistry of Heterocyclic Compounds" (reviewed by R. ROBINSON) 190
P. B. D. DE LA MARE and J. H. RIDD: "Aromatic Substitution: Nitration and Halogenation" (reviewed by R. ROBINSON) 190
A list of some of the papers to be published in future issues 192

NUMBER 4

C. A. COULSON: Bond lengths in the cyclo-octatetraene dianion $C_8H_8^{--}$. 193
S. K. BALASUBRAMANIAN: Studies in stereochemistry—I. Stereospecific routes to *trans- anti-* and *cis-syn*-Δ^8-dodecahydrophenanthrenes 196
JEAN HAEUSER et RENÉ LOMBARD: Isolement et structure d'un nouveau diterpène: l'acide daniellique 205
FLORENCE LEDERER et GUY OURISSON: Stéréochimie de l'acide daniellique . 205
R. HODGES: Some ketomanoyl oxides 215
N. PETRAGNANI: Aryl tellurium trihalides—II. Condensation reaction with methylketones and aromatic compounds containing electron-repelling groups 219
J. B. LEE and M. M. EL SAWI: Sugar esters—I. Oxide formation in the synthesis and hydrolysis of some fluorides and phosphate esters 226
F. B. ANDERSON and D. H. LEABACK: Substrates for the histochemical localization of some glycosidases 236
KATSUMI KOTERA: The stereochemistry of lycorane—II. (−)β-Lycorane . 240
KATSUMI KOTERA: The stereochemistry of lycorane—III. γ- and δ-Lycorane 248
T. KAMIKAWA and T. KUBOTA: Natural furan derivatives—VII. The presence of a seven-membered α,β-unsaturated lactone in obacunone 262
T. MATSUURA, T. KAMIKAWA and T. KUBOTA: Natural furan derivatives—VIII. Relationship between the furan ring and six- and seven-membered lactone rings in obacunone 269
Book Review:
J. A. DEAN: "Flame Photometry" (reviewed by J. MACINTYRE) . . 277
Erratum:
J. W. POWELL and M. C. WHITING: The decomposition of sulphonylhydrazone salts: mechanism and stereochemistry—II. The pyrolysis of the diazodecalins 278
Papers to be published in a forthcoming issue: "Proceedings of a Conference on Rotatory Dispersion: Related Theory and Application" 279
Subject, Author and Title Index to *Tetrahedron*, Volumes 8 to 11, and *Tetrahedron Letters*, Numbers 1 to 27, 1960.

VOL.
12
1961

VOL
12
196

Tetrahedron, 1961, Vol. 12, pp. 1 to 6. Pergamon Press Ltd. Printed in Northern Ireland

ETUDES SUR LES METHODES DE PREPARATION DE LA SELENOCYSTAMINE, SELENOHYPOTAURINE ET SELENOTAURINE

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VOL. 12 1961

Résumé—Le chlorhydrate de la sélénocystamine (ou β-β'-diaminodiéthyldiséléniure) a été préparé au départ de sélénocyanure de potassium et de N-bromoéthylphtalimide avec un rendement global de 40% environ. L'oxydation du chlorhydrate de la sélénocystamine par l'eau de brome conduit à la sélénohypotaurine (acide aminoéthanesélénique) avec un rendement de 97%. D'autres voies d'accès à la sélénohypotaurine, soit à partir du phtalimidoéthanesélénocyanure, soit de l'acide chloroéthane sélénique sont également décrites mais aboutissent à des résultats négatifs. L'oxydation de la sélénocystamine ou de la sélénohypotaurine par l'eau de chlore, à chaud, conduit à la sélénotaurine (acide aminoéthane sélénonique) qui n'a pas pu être isolée à l'état pur, cristallisé, par suite de son instabilité.

EN vue de comparer les métabolismes de produits organiques soufrés et séléniés, il nous a été demandé de synthétiser les analogues séléniés de la cystamine, de l'hypotaurine et de la taurine.*

Seule la "sélénocystamine" ou $\beta\beta'$-diamino diéthyl diséléniure parait avoir déjà été synthétisée.[1] La "sélénohypotaurine" ou acide amino-2 éthane séléninique et la "sélénotaurine" ou acide amino-2 éthane sélénonique par contre, n'ont pas, à notre connaissance, été décrits dans la littérature. Les composés organiques séléniés ont fait l'objet d'une importante et récente monographie.[1b]

La matière première choisie pour le présent travail est le sélénocyanure de potassium.[2]

(A) *Sélénocystamine*

La méthode utilisée est celle de Coblentz[1]. Le mode opératoire a été précisé.

Le sélénocyanure de potassium (I) et le bromo-1 phtalimido-2 éthane, dans l'acétone, selon[3] donnent le phtalimido-2 éthane sélénocyanure (II). L'hydrolyse par la soude conduit au composé III lequel, chauffé avec l'acide chlorhydrique concentré, fournit la "sélénocystamine" (IV). Il n'est pas nécessaire d'opérer en tube scellé pour effectuer cette dernière opération.

La pureté de IV a été contrôlée par analyse chromatographique. L'identité a été établie par dosage iodométrique du groupement diséléniure et par analyse élémentaire.

(B) *Sélénohypotaurine*

Trois méthodes de préparation ont été explorées. Seule la première a donné de bons résultats. Les autres ne constituent que des modes de formation.

* Préparations entreprises à la demande du service de Biologie du C.E.A.

[1] V. Coblentz, *Ber. Dtsch. Chem. Ges.* **24**, 2134 (1891).
[2] G. R. Waitkins et R. Shutt, *Inorg. Synth.* **2**, 189 (1946).
[3] H. Brintzinger, K. Pfannstiel et H. Vogel, *Z. Anorg. Allg. Chem.* **256**, 75 (1948).
[4] T. O. Soine et M. R. Buchdahl, *Org. Synth.* **32**, 18 (1952).

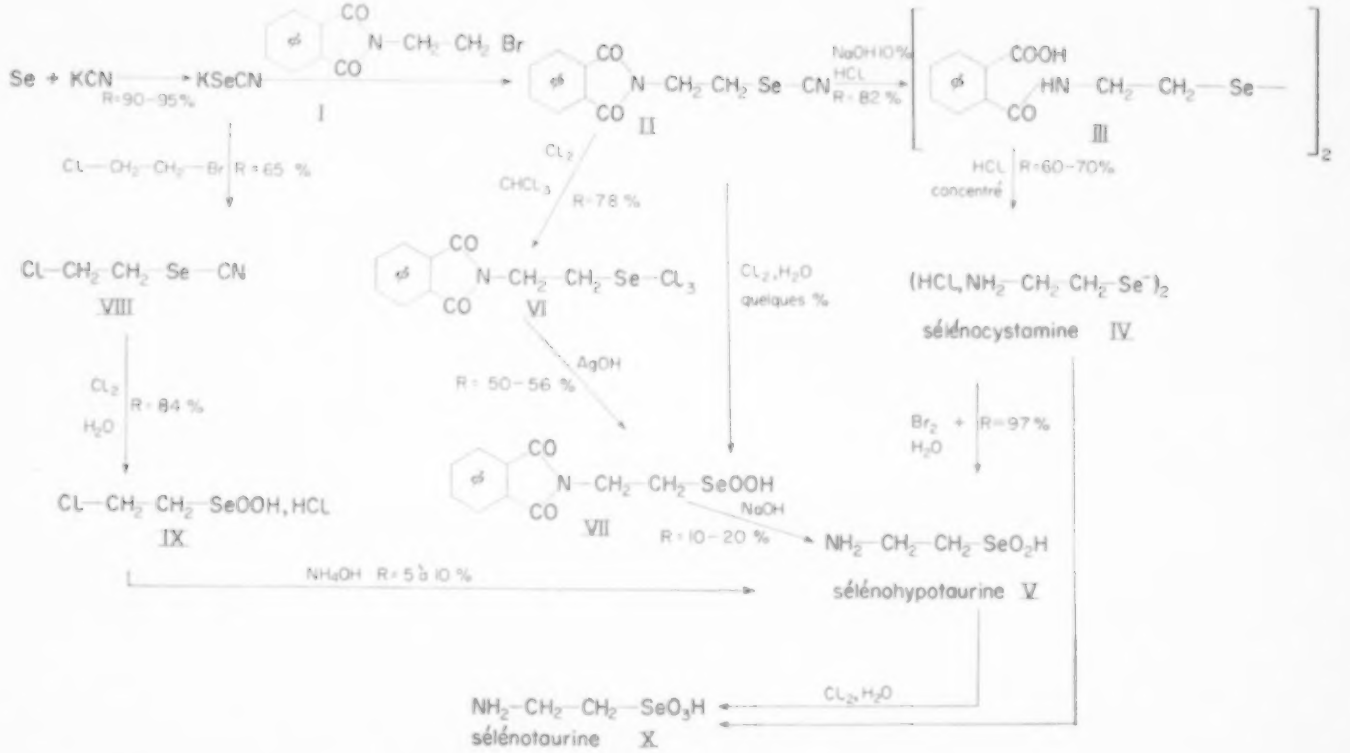

FIG. 1.

VOL. 1
1
1964

(1) *Par oxydation de la "sélénocystamine"*. L'oxydation du groupement diséléniure R—Se—Se—R en acide séléninique R—SeO_2H peut être effectuée au moyen de divers réactifs. Nous avons essayé les suivants sur le chlorhydrate de la sélénocystamine (IV):

—HNO_3 selon;[5,6] il se forme un mélange de sélénohypotaurine (V) et de sélénotaurine (X) bien que IV ne soit pas entièrement oxydé.

—H_2O_2 selon;[5] on obtient le même résultat.

—l'eau de brome à froid; l'oxydation est quantitative. On élimine ensuite HBr par passage sur une résine échangeuse Dowex 50 × 12 forme H^+. L'élimination de HBr est indispensable, car V porté à sec en milieu acide se décompose et libère du sélénium.

La "sélénohypotaurine" se comporte sur résine Dowex 50 comme l'hypotaurine.[14] La pureté du produit a été contrôlée par chromatographie sur papier et l'identité établie par dosage iodométrique de la fonction séléninique et analyse élémentaire.

(2) *A partir de l'acide phtalimido-2 éthane séléninique* (VII). L'oxydation directe de II en acide phtalimido-2 éthane séléninique (VII) n'a donné qu'un rendement très faible. VII a donc été préparé par une voie détournée, par l'intermédiaire de VI selon des techniques décrites dans.[3,7]

Aucune des méthodes connues d'élimination du groupement phtalyle n'a été satisfaisante. Le traitement à l'hydrazine[8] provoque la réduction de la fonction séléninique en diséléniure.[9] Le chauffage avec l'acide chlorhydrique détruit la molécule avec libération de sélénium. L'hydrolyse à chaud par la soude concentrée conduit finalement à un produit impur et très instable.

(3) *Par amination de l'acide chloro-2 éthane séléninique* (IX). L'addition d'une solution acétonique de sélénocyanure de potassium (I) au chloro-1 bromo-2 éthane, donne le chloro-2 éthane sélénocyanure (VIII) avec un rendement de 63%. L'opération inverse préconisée par[3] provoque la formation prépondérante du disélénocyanoéthane. VIII a été oxydé en acide chloro-2 éthane séléninique (IX) selon.[3]

L'amination de IX soit par l'ammoniac liquide soit par l'ammoniaque concentré n'a pas donné de résultats satisfaisants.

(C) *Sélénotaurine*

L'oxydation des acides séléniniques R—SeO_2H en acides sélénoniques R—SeO_3H a été réalisée par divers réactifs.[10] Nous avons essayé les procédés suivants pour l'oxydation de la sélénohypotaurine en sélénotaurine (X):

—par $KMnO_4$ en milieu alcalin selon;[10] l'oxydation ne se fait que partiellement, sans décomposition. En poussant l'oxydation la proportion de V diminue, mais (X) se décompose presque totalement. En milieu acide on obtient les mêmes résultats.

—par HNO_3 selon;[10] nous avons eu les mêmes résultats.

—par H_2O_2 dilué selon;[5] nous avons pu observer la formation de traces de X. En milieu plus concentré, il y a décomposition.

L'oxydation du groupement diséléniure R—Se—Se—R en R—SeO_3H peut être

[5] E. P. Painter, K. N. Frank et R. A. Goertner, *J. Org. Chem.* **5**, 578 (1940).
[6] E. H. Shaw et E. R. Reid, *J. Amer. Chem. Soc.* **48**, 520 (1926).
[7] H. J. Backer et H. J. Winter, *Rec. Trav. Chim. Pays-Bas* **56**, 501 (1937).
[8] F. E. King et D. A. A. Kidd, *J. Chem. Soc.* 3315 (1949).
[9] H. Rheinboldt et E. Giesbrecht, *Chem. Ber.* **88**, 666 (1955).
[10] M. L. Bird et F. Challenger, *J. Chem. Soc.* 572 (1942).

obtenue[11] par le chlore à 50–60° dans le cas des produits séléniés aromatiques. Intermédiairement cette oxydation doit passer par le stade $R—SeO_2H$. Nous avons aussi appliqué cette méthode à IV et à V. Dans les deux cas l'oxydation se fait complètement et X formé ne se décompose que faiblement. Un dosage de X, directement dans le milieu réactionnel, indique un rendement de l'ordre de 75–80%.

Comme la taurine, la sélénotaurine (X) est un produit acide. En effet, il n'est pas fixé par la résine Dowex 50 × 12 forme H^+. Il est, au contraire, fixé par la résine Dowex 2 forme OH^-. Il est très peu stable, même en solution diluée, et se réduit très facilement. Le dosage est effectué par réduction par HI en sélénocystamine. La sélénocystamine formée peut être alors dosée par I_2, ce qui permet de confirmer le premier dosage. Nos essais d'obtention de la sélénotaurine à l'état cristallisé ont échoué. X porté à sec, sous vide à basse température, en présence de HCl, se réduit avec libération de chlore. Nous avons essayé d'éliminer HCl par AgOH, mais X donne un sel d'argent peu soluble dans l'eau et le rendement d'isolement est inférieur à 5%. Par chromatographie sur alumine le rendement est du même ordre.

Les traces de X que nous avons ainsi isolées se présentent sous forme de cristaux blancs qui, en quelques heures, sont décomposés en donnant du sélénium et de la sélénohypotaurine (V).

TABLEAU DE *Rf*

Produits	Solvants de chromatographie			
	n Butanol 75 Acide formique 15 Eau 10	n Butanol 1 Pyridine 1 Eau 1	Ethanol 90 NH_4OH 22% 10	Phénol 80 Eau 20
Sélénocystamine	0·08	0·55	0·64	
Sélénohypotaurine	0·15	0·20	0·12	0·68
Sélénotaurine	0·02	0·29	0·20	0·21
Hypotaurine	0·07	0·29		0·63
Taurine	0·05	0·36		0·29

Comparaison entre les *Rf* des produits séléniés et soufrés correspondants sur papier Whatman no. 1. Les *Rf* des produits soufrés sont ceux de la littérature.[12]

PARTIE EXPERIMENTALE*†

Séléno cyanure de potassium (I). Préparé selon.[3] On mélange 24·5 g (0·3 M) de sélénium (99%) en poudre, sec, avec 22 g (0·33 M) de KCN sec, pulvérisé. Ce mélange chauffé, avec agitation, en atmosphère de N_2, fond vers 145°; le chauffage est poursuivi deux heures à 160°. On obtient une pâte grise qui se prend en masse par refroidissement. Cette masse est reprise par 200 cc d'acétone anhydre. On chasse l'excès d'acide cyanhydrique par un courant de CO_2 sec et filtre le précipité de K_2CO_3 contenant un peu de Se n'ayant pas réagi. La solution acétonique de KSeCN rosit rapidement puis laisse un dépôt de Se rouge si elle n'est pas soigneusement protégée de l'humidité. En concentrant, KSeCN précipite en cristaux blancs qui sont stables à sec. On peut doser la solution acétonique par argentimétrie. Le rendement est de 90–95%. Il est préférable d'utiliser directement cette solution dans les étapes suivantes.

Phtalimido-2 éthane sélénocyanure (II). Préparé selon.[3] 28 g (0·11 M) de phtalimido-2 bromo-1

* Les points de fusion ont été déterminés au banc chauffant Kofler.
† Microanalyses par Mme Duvernier.

[11] M. Stoecker et F. Krafft, *Ber. Dtsch. Chem. Ges.* **39**, 2200 (1906).
[12] E. Bricas, F. Kieffer et Cl. Fromageot, *Biochim. Biophys. Acta* **18**, 358 (1955).

éthane[4] sont dissouts dans 50 cc d'acétone anhydre à l'ébullition. On y ajoute 170 cc de solution acétonique de KSeCN 0·65 N. On chauffe 3 heures à reflux; peu à peu KBr précipite et la solution devient jaune. A la solution froide on ajoute 1000 cc d'eau; KBr se dissout et II précipite en cristaux blancs. On obtient 28·5 g de II soit 92%.

II est un produit blanc, cristallisé, inodore qui se conserve bien à sec F = 127°.

Analyse: $C_{11}H_8O_2NSe$ Calc. %: C 47·32 H 2·89 N 10·03
47·42 3·03 9·59

Il est à remarquer que pour sécher ce produit, ainsi que les suivants, l'anhydride phosphorique en dessicateur, sous vide, provoque une décomposition rapide. Pour remédier à cet inconvénient, on remplace le P_2O_5 par de l'"Actigel" ou du tamis moléculaire "Linde" type 4A.

Bis [*β*-(*o-carboxybenzamido*) *éthyl*] *diséléniure* (III). Préparé selon.[1] 2·8 g (10 mM) de II sont mis en suspension dans 20 cc de NaOH à 10%. La suspension est chauffée à 90–95° avec agitation. Au bout de 15 minutes la dissolution de II est complète. Une gomme jaune se sépare puis cristallise lentement. Au bout de 24 heures au réfrigérateur, la cristallisation est achevée. On obtient 2·25 g de III soit un rendement de 82%. (III) est un produit jaune, cristallisé, qui se décompose à 110° en donnant du sélénium rouge. F: 118–119° (dioxanne). Pour l'opération suivante on peut utiliser le produit brut.

Dichlorhydrate de "Séléno cystamine" (IV). 2 g (37 mM) de III sont dissouts dans un mélange de 1 ml d'acide acétique et 4 ml d'acide chlorhydrique concentré. On chauffe à reflux pendant 3 heures. Après traitements habituels on obtient le produit cherché par cristallisation dans l'alcool avec un rendement de 60 à 70%.

Le groupement diséléniure, dosé selon l'équation: $(R—Se)_2 + 6I + 8NaHCO_3 \rightarrow 2R — SeO_2Na + 6NaI + 8CO_2 + 4H_2O$ correspond à une pureté de 98%.

Analyse: $C_4H_{14}N_2Cl_2Se_2$: calc. % C 15·06 H 4·42 N 8·78
14·65 4·41 8·47

"*Sélénohypotaurine*" (V). 3·2 g (10 mM) de IV sont dissouts dans 20 cc d'eau. On ajoute lentement, sous refroidissement, la quantité stoéchiométrique d'eau de brome. L'analyse chromatographique de cette solution montre que l'oxydation est complète. Cette solution est placée sur une colonne de résine échangeuse Dowex 50 × 12 forme H^+ (dimensions h = 20 cm, ϕ = 2·4 cm). On lave à l'eau jusqu'à élimination des ions Br^-, puis on élue la sélénohypotaurine par NH_4OH 2N. Cette élution est rapide. On isole V de la solution ammoniacale par lyophilisation sous vide poussé. On obtient 3 g de V soit 96% de rendement. V est un produit blanc cristallisé, stable à l'abri de l'humidité. L'analyse par chromatographie sur papier ne révèle pas la présence d'impuretés. V se décompose instantanément à 150–152° en donnant du sélénium, mais dès 130° il commence à jaunir et se décomposer lentement. Le dosage de la fonction séléninique indique une pureté de 99·3%. Ce dosage est basé sur la réaction:

$$2R—SeO_2H + 6HI \rightarrow (R—Se—)_2 + 3I_2 + 4H_2O$$

et la technique utilisée est sommairement décrite dans:[13]

Analyse: $C_2H_7O_2NSe$: Calc. % C 15·39 H 4·52 N 8·97
14·75 4·92 8·52

Trichloroséléno-1 phtalimido-2 éthane (VI). 0·5 g (1·8 mM) de II sont dissouts dans 7 cc de chloroforme sec. On fait arriver, bulle à bulle, un courant de chlore sec. La solution se colore en jaune; au bout d'une heure trente, il se forme un précipité blanc cristallisé. Au bout de trois heures, le courant de chlore est remplacé par un courant d'azote sec pour éliminer l'excès de chlore. On ajoute au mélange réactionnel 15 cc d'éther anhydre. On filtre le précipité et le sèche sous vide. On obtient 0·5 g de VI, soit un rendement de 78%. VI est un produit blanc cristallisé, F = 155–157° (décomposition). VI est très peu stable et libère rapidement du chlore, du sélénium et de l'hydrogène sélénié.

Analyse: $C_{10}H_5O_2NSeCl_4$: Calc. % C 33·10 H 2·24 Cl 29·58
33·18 2·33 28·00

Acide phtalimido-2 éthane séléninique (VII). Dans une suspension de AgOH, préparée à partir de 6 g de nitrate d'argent cristallisé et de 35 cc de NaOH N, on verse une solution de 4·2 g de VI dans

[13] H. Rheinbolt dans Houben-Weyl, *Methoden der Organische Chemie* Vol. 9, p.1104. G. Thieme Verlage, Stuttgart (1955).

100 cc d'alcool à 50%. Cette suspension est agitée énergiquement. Au bout de 3 heures on filtre AgCl et l'excès de AgOH.

Le filtrat est évaporé à sec sous vide. Le résidu est repris par 2 cc d'eau glacée. On filtre, sèche et l'on obtient 1·7 g de VII, soit un rendement de 50%.

VII est un produit blanc, cristallisé, inodore, F = 176°. Il est stable et ne nécessite pas de précautions particulières quant à son emploi.

Analyse: $C_{10}H_9O_4NSe$: Calc. % C 41·98 H 3·17
41·88 3·26

Essai d'hydrolyse de (VII). 1 g de l'acide VII et 10 ml de NaOH à 50% sont chauffés à 60–70° pendant 4 heures en atmosphère d'azote. Après acidification et filtration de l'acide phtalique on élimine les ions Na^+ sur une colonne de résine échangeuse Dowex 50 X–12 forme H^+. V est élué de la colonne par NH_4OH 2N. Le produit obtenu, avec un faible rendement, est impur et instable.

Chloro-1 sélénocyano-2 éthane (VIII). A une solution de 5·9 g (41 mM) de bromo-1 chloro-2 éthane dans 6 ml d'acétone, on ajoute en 30 minutes 5·4 g (38 mM) de KSeCN en solution dans 54 ml d'acétone. Après chauffage à reflux pendant 1 heure 20 on traite le mélange réactionnel.[3] VIII est obtenu avec un rendement de 63%. $E_{1\cdot5mm}$ = 74–75°.

Chlorhydrate de l'acide chloro-2 éthane séléninique (IX). Préparé selon[3] avec un rendement de 84% au départ de 8·6 g de VIII. F = 86° (dioxanne). IX est stable quand il est conservé à l'abri de l'humidité.

Analyse: $C_2H_4O_2SeCl_2$: Calc. % C 11·33 H 2·85
11·49 3·05

Essai d'amination de (IX). 1·75 g (8 mM) de IX en solution dans 10 ml de NH_4OH à 20% sont chauffés à l'autoclave pendant 3 jours à 65–70°. Après traitement sur résine échangeuse Dowex 50 × 12 forme H^+ on obtient une fraction dont le dosage iodométrique indique la présence de faibles quantités d'hypotaurine (V).

Sélénotaurine (X). On fait barboter un courant de chlore jusqu'à saturation du milieu dans une solution de 1 mM de IV ou de 2 mM de V dans 5 cc d'eau, chauffée au B.M. à 55°. On élimine ensuite l'excès de chlore par un courant d'azote. L'analyse du milieu réactionnel par chromatographie sur papier donne 2 taches révélées par la ninhydrine. Par passage sur résine échangeuse Dowex 50 × 12 forme H^+, on élimine l'impureté. Le groupement sélénonique est dosé selon l'équation:

$$2R-SeO_3H + 10HI \rightarrow (R-Se-)_2 + 5I_2 + 6H_2O$$

ce dosage peut être contrôlé par détermination du diséléniure formé.

Le rendement en X ainsi déterminé sur la solution acide est de 75 à 80%.

Cette solution placée au réfrigérateur ne se conserve pas. Au bout de quelques jours, la chromatographie montre qu'il y a une réduction partielle en V.

Essai d'isolement de (X) *par élimination de* HCl *par* AgOH. A la solution précédente on ajoute un léger excès de AgOH. On agite la suspension 1 heure. Le précipité de sel d'argent est filtré puis lavé à l'eau chaude; par refroidissement le filtrat se trouble. On élimine Ag^+ par filtration sur une colonne de Dowex 50 × 12 forme H^+. X est élué rapidement par l'eau. L'éluat est ensuite lyophilisé sous vide poussé. On obtient quelques cristaux blancs qui se décomposent et deviennent rouges au bout de 2 à 3 heures.

Ces cristaux se décomposent vers 130–135° en donnant un léger dégagement gazeux (microscope Kofler). Au banc Kofler, il y a décomposition instantanée à 160° avec formation de sélénium.

[14] L. Pichat et M. Herbert, *Bull. Soc. Chim.* 820 (1958).
[15] H. Rheinbolt dans Houben-Weyl, *Methoden der Organische Chemie* Vol. 9, p. 917–1204. Thieme Verlage, Stuttgart (1955).
[16] H. Rheinbolt, dans Houben-Weyl, *Methoden der Organische Chemie* Vol. 9, p. 1124–1128. Thieme Verlage, Stuttgart (1955).

Tetrahedron, 1961, Vol. 12, pp. 7 to 12. Pergamon Press Ltd. Printed in Northern Ireland

VOL. 12 1961

ADDITIONSREAKTIONEN DER NITROSOGRUPPE—II*

DIELS–ALDER-REAKTION MIT CYCLISCHEN DIENEN; SYNTHESE EINIGER *CIS*-4-PHENYLAMINOCYCLANOLE

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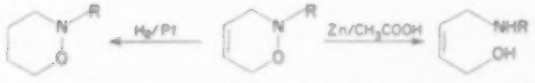
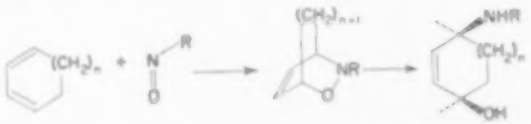
Abstract—By Diels-Alder-reaction of nitroso benzene with cyclic dienes or cycloheptatriene, some bicyclic 1.2-oxazines were prepared. The reduction of these compounds yields, with cleavage of the N—O-bond, *cis*-1.4-amino cyclenols.

Zusammenfassung—Durch Diels–Alder-Reaktion von Nitrosobenzol mit cyclischen Dienen bzw. Cycloheptatrien werden einige bicyclische 1.2 -Oxazine dargestellt, deren Reduktion unter Aufspaltung der N—O-Bindung zu *cis*-1.4-Aminocyclenolen führt.

Die Fähigkeit von N—O-Bindungen, als Dienophil bei Diels–Alder-Reaktionen zu fungieren, hat wohl zuerst Dilthey[1] am Spezialfall der Umsetzung von Nitrosobenzol mit Phencyclon und Tetracyclon beobachtet. Die Allgemeingültigkeit der Reaktion bewiesen dann Wichterle[2] und Arbusow[3], die auch die Hydrierung und Reduktion der Addukte beschrieben:



Als cyclisches Dien war hierbei nur das Cyclohexadien untersucht worden,[3c,d] hier schien uns jedoch gerade eine präparative Anwendung der Umsetzung möglich zu sein: Da die Zn-Reduktion der Addukte ohne Berührung der C—O- und C—N-Bindung erfolgt, sollten aus den bicyclischen Oxazinen stereospezifisch alicyclische *cis*-1.4-Aminoalkohole gewonnen werden können:



* Die in den *Chem. Ber.* **89**, 1412 (1956) veröffentlichte Arbeit soll als erste Mitteilung gelten.

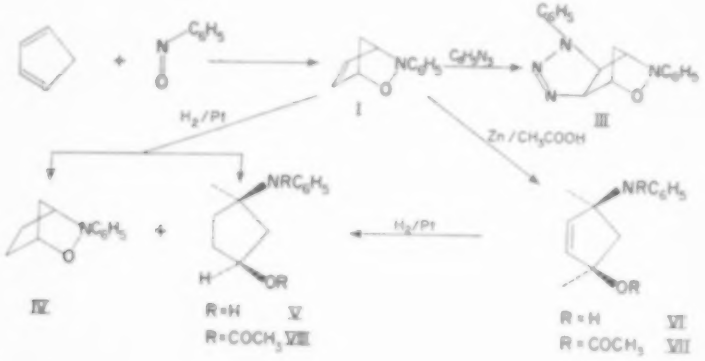
[1] W. Dilthey, *J. Prakt. Chem. (N.F.)* **156**, 27 (1940);

[2a] O. Wichterle, *Coll. Trav. Chim. Tchéc.* **12**, 292 (1947); [b] O. Wichterle und V. Gregor, *Chem. Listy* **51**, 605 (1957) und früher.

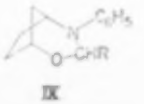
[3a] Yu. A. Arbusow, *Nachr. Akad. Wiss. U.S.S.R.* **60**, 993 (1948); [b] Yu. A. Arbusow und A. Pisha, *Nachr. Akad. Wiss. U.S.S.R.* **116**, 71 (1957) und früher; [c] Yu. A. Arbusow, A. J. Finkelstein und P. P. Shorygin, *J. Phys. Chem.* (Moskau) **24**, 802 (1950); [d] Yu. A. Arbusow und T. A. Masstrjukowa, *Ber. Akad. Wiss. U.S.S.R.* 665 (1952).

Wir haben daher die Reaktion verschiedener cyclischer Diene mit Nitrosobenzol untersucht.

Cyclopentadien reagiert leichter als Cyclohexadien, die Lösung in Äther bei 0° wird bereits im Verlauf einer Stunde entfärbt. Das Addukt, 3-Phenyl-2-oxa-3-azabicyclo-[2.2.1]-hepten-(5) (I) ist—wahrscheinlich wegen der Ringspannung—besonders im unreinen Zustand recht instabil, in Lösung tritt bei Zimmertemperatur meist völlige Rückspaltung in die Komponenten ein. Das Cyclohexadienaddukt, 3-Phenyl-2-oxa-3-azabicyclo-[2.2.2]-octen-(5) (II) spaltet dagegen auch in siedendem Benzol erst teilweise auf. Die Doppelbindung im spannungsreichen Bicyclus von I reagiert mit Phenylazid, das entstehende Hydrotriazol (III) ist stabil. Für das Vorliegen einer erheblichen Ringspannung spricht auch der Verlauf der Hydrierung bei −5° in Gegenwart von Pt-Kohle: das gesättigte Oxazin (IV) ist nur eines der Hydrierungsprodukte, es konnte nur unrein gewonnen werden; daneben werden als Folgeprodukt der Ringspaltung 3-N-Phenylaminocyclopentanol (V) und als Reduktionsprodukt des durch Rückspaltung gebildeten Nitrosobenzols Anilin gefunden. Auch bei der Reduktion mit Zn in Essigsäure-Äther bei 0° macht sich die Rückspaltung des Adduktes I bemerkbar: hier treten neben 4-N-Phenylaminocyclopenten-(2)-ol-(i) (VI) Hydrazobenzol und Anilin als Produkte auf. Das Diacetylderivat (VII) von VI kann seinerseits leicht zu dem entsprechenden V-Derivat (VIII) hydriert werden.



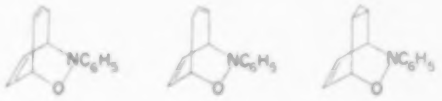
Bei V kann nun die *cis*-Stellung der Substituenten leicht bewiesen werden: nur aus dieser Stellung heraus ist bei der Umsetzung mit Aldehyden ein erneuter Ringschluss zum bicyclischen 1.3-Oxazin, IX, möglich, wir erhielten die Stammverbindung bei der Reaktion von V mit Formalinlösung.



IX

Die Umsetzungen beim *Cyclohexadien* verlaufen analog, auf diese Weise sind aus dem N-Phenyl-2-oxa-3-azabicyclo-[2.2.2]-octen-(5) (II) *cis*-4-Phenylaminocyclohexen-(2)-ol-(1) (X) und der entsprechende gesättigte Aminoalkohol zugänglich. Dagegen schlugen Versuche, *Furan* als Dien bei der Diels–Alder-Reaktion mit Nitrosobenzol einzusetzen, fehl.

Während die Diensynthese von Nitrosobenzol mit Cyclopentadien und Cyclohexadien unter milden Bedingungen glatt und leicht verläuft, konnte bei *Cycloheptadien* nach analogem Verfahren auch bei langer Versuchsdauer keine Addition erreicht werden. Dagegen reagierte *Cycloheptatrien*,* wenn auch langsam und in mässiger Ausbeute. Für das Addukt kommen 3 Konstitutionsformeln in Frage: Neben den beiden "normalen" XIIa und XIIb, die sich in der Lage der zweiten Doppelbindung unterscheiden, sollte eine dritte, XIIc, möglich sein, bei der das Trien als Norcaradien reagiert. Eine solche Reaktionsweise war von Alder und Jacobs[4] bei den Diensynthesen von Cycloheptatrien mit Acetylendicarbonsäureester und mit Maleinsäureanhydrid nachgewiesen worden.



XII a XII b XII c

Zur Entscheidung haben wir die gleichen Reaktionen, wie sie Alder und Jacobs beschreiben, auch bei unserem Addukt durchgeführt:

Reaktion	Verhalten des Cycloheptatrienadduktes	
	mit Maleinsäureanhydrid (M) bzw. Acetylendicarbonsäureester (A)	mit Nitrosobenzol
Hydrierung in Gegenwart von PtO_2	(M) Dihydroderivat	Tetrahydroderivat (XIII)
Hydrierung in Gegenwart von Raney-Ni	bei Atmosphärendruck (M,A): Dihydroderivat; bei 100° und 150° at Tetrahydroderivat mit Endocyclopropylengruppe	bei Atmosphärendruck XIII, daneben gesättigter Aminoalkohol (XIV)
Oxydation mit Permanganat	Cyclopropandicarbonsäure	(bei der Diacetylverbindung des ungesättigten Aminoalkohols XV): Acetanilid

Das Cycloheptatrien–Nitrosobenzoladdukt verhält sich also anders als die ähnlich gewonnenen carbocyclischen Verbindungen: es werden sowohl bei Hydrierung an PtO_2 als auch mit Raney-Ni 2 Mol H_2 aufgenommen, das Produkt XIII ist als 2-Oxa-3-azabicyclo-[3.2.2]-nonan aufzufassen; bei der Oxydation des Diacetylderivats des Aminoalkohols XV, der durch Zn-Staub-Essigsäure-Reduktion aus XII entsteht, konnten keine Bruchstücke gefasst werden, die noch den Cyclopropanring enthalten.

Zur Klärung der Struktur wurde ferner das Protonenresonanzspektrum von XII

* Wir danken der Deutschen Shell AG., Hamburg, für die Überlassung dieses Produkts.

[4] K. Alder und G. Jacobs, *Chem. Ber.* **86**, 1528 (1953).

in CS_2 und CCl_4 aufgenommen und mit dem des Cyclohexadienderivats II verglichen.* Die beiden Spektren unterscheiden sich ausserordentlich, für die endo-Propenostruktur XIIa bzw. b des Cycloheptatrienadduktes spricht:

—es treten ausser einem Signal bei 101 Hz (bezogen auf H_2O 40 M H_2), das den CH_2—C═C-Protonen zuzuordnen ist, keine Resonanzen über 100 Hz auf. Die Signale des Cyclopropylsystems liegen allgemein bei 180 Hz.

Im Spektrum von II tritt bei 16 Hz *eine* Signalgruppe auf, die nach Lage und Stärke zu den beiden, dem N-bzw.O-Atom benachbarten CH-Gruppen gehören muss. Im Spektrum von XII findet man an dieser Stelle *zwei* getrennte Signale, weil nunmehr (bei Annahme der endo-Propenostruktur) die elektronische Abschirmung der einen CH-Gruppe durch die benachbarte Doppelbindung verändert ist. Die Endo-Cyclopropylenstruktur hätte die gleiche "Symmetrie" wie das Cyclohexadienderivat II.

Wir halten aus diesen Gründen XII für das N-Phenyl-2-oxa-3-azabicyclo-[3.2.2]-nonadien, wobei zwischen den isomeren Formen XIIa und b noch nicht entschieden werden kann. Die Zn-Staub-Eisessig-Reduktion des gesättigten bicyclischen Oxazins XIII liefert *cis*-4-Phenylaminocycloheptanol (XIV). Über die Stereochemie der Addukte und die Kinetik ihrer Bildung soll später berichtet werden.

EXPERIMENTELLER TEIL

N-Phenyl-2-oxa-3-azabicyclo-[2.2.1]-hepten-(5) (I)

5·35 g Nitrosobenzol wurden in 50 ml Äther gelöst, die Lösung wurde auf 0° gekühlt, 4·1 g frisch destilliertes Cyclopentadien zugefügt und die Lösung bei 0° stehen gelassen. In einer Stunde ging die grüne Farbe der Lösung bis auf gelb zurück; nach 2 Stunden wurden der Äther und das überschüssige Cyclopentadien abgesaugt. Der schmierige Rückstand kristallisierte beim Anreiben mit Alkohol, durch Umkristallisieren aus wenig Alkohol bei −70° wurden 6·8 g I (78% d.Th.) gewonnen, F.32–34°. Die Substanz zersetzt sich bei Raumtemperatur allmählich. (Gef. C, 75·61; H, 6·52; N, 8·06; $C_{11}H_{11}NO$ erfordert: C, 76·27; H, 6·40; N, 8·08%).

Phenylazidaddukt (III)

0·5 g I wurden in 0·5 g Phenylazid gelöst. Nachdem die Lösung 24 Stunden bei 0° gestanden hatte, setzte Kristallabscheidung ein, nach 48 Stunden war der grösste Teil der Probe erstarrt. Aus Petroläther umkristallisiert, schmolz das Addukt bei 143–144°. (Gef. C, 70·30; H, 5·58; N, 19·51; $C_{17}H_{16}N_4O$ erfordert: C, 69·86; H, 5·52; N, 19·17%).

Hydrierung von I

Zur Hydrierung wurde I nicht erst isoliert, vielmehr wurde zu einer Lösung von 4 g Nitrosobenzol in 40 ml Äther und 4 g Cyclopentadien nach der Entfärbung 1 g Platin-Kohle zugesetzt und dann die Lösung im Eis-Salz-Bad bei Atmosphärendruck hydriert. Statt der berechneten 1880 ml wurden in 8 Stunden 2740 ml H_2 aufgenommen. Nach dem Abfiltrieren des Katalysators und Absaugen des Äthers wurde der Rückstand im Vakuum bei 1 mm Druck destilliert. Es wurden aufgefangen: (a) Vorlauf bis 100° (grösstenteils bei ca. 45°), 1 g, hauptsächlich Anilin, charakterisiert durch IR-Spektrum, (b) Kp_1, 116–126°, 2 g. Durch einen Begleitstoff, der sich auch durch erneute Destillation nicht entfernen liess, war diese Fraktion stark orange gefärbt. Nach dem IR-Spektrum sollte es sich um *N-Phenyl-2-oxa-3-azabicyclo-[2.2.1]-heptan* (IV) handeln. Eine ein zweites Mal destillierte Probe mit $Kp_{1\cdot5}$124° war noch verunreinigt: (gef. C, 76·89, H, 7·60, N, 9·73. $C_{11}H_{13}NO$ erfordert: C, 75·40, H, 7·47, N, 8·00%) (c) Kp_1 150–155°, 2 g cis-3-N-*Phenylaminocyclopentanol* (V). Eine Probe wurde mit Natriumacetat und Acetanhydrid 1 Stunde auf 140° erhitzt und dann mit verd. Natronlauge neutralisiert. Der Niederschlag wurde abfiltriert und aus Petroläther umkristallisiert.

* Wir danken der Badischen Anilin-u. Sodafabrik, Ludwigshafen, u. Herrn Dr. Bügel für die Aufnahme und Auswertung der Spektren.

Diacetat VIII F. 79–81° (Gef. C, 69·59; H, 7·40; N, 5·52; $C_{15}H_{19}NO_3$ erfordert: C, 68·94; H, 7·33; N, 5·36%).

Reduktion von I. Auch zur Reduktion wurde I nicht erst isoliert. Zu einer Lösung von 5 g Nitrosobenzol in 50 ml Äther und 5 g Cyclopentadien wurden nach der Entfärbung 50 ml Eisessig zugefügt und in die bei 0° gehaltene Lösung allmählich 13 g Zinkpulver eingetragen. Die Lösung stand dann noch eine Stunde bei 0° und 30 Minuten bei Raumtemperatur. Sie wurde mit 40 g NaOH in 100 ml Wasser alkalisch gemacht und dann zur Abtrennung flüchtiger Bestandteile der Wasserdampfdestillation unterworfen. Im Destillat wurden 2 g Anilin als Acetanilid, F.114°, identifiziert. Das Wasser-Zinkoxydgemisch wurde filtriert, der Rückstand mit 50 ml warmem Benzol ausgewaschen und das Filtrat mit diesem Benzol ausgeschüttelt. Das Benzol wurde über $CaCl_2$ getrocknet und abgesaugt. Der Rückstand wurde in wenig Alkohol aufgenommen und diese Lösung in der Wärme mit Wasser versetzt, bis Trübung eintrat. Beim Abkühlen schieden sich Kristalle aus, 0·5 g F.124–126°, nach IR-Spektrum und Analyse Hydrazobenzol. Beim weiteren Versetzen der alkoholischen Lösung mit Wasser schied sich ein Öl ab. Die Emulsion wurde mit Benzol ausgeschüttelt, das Benzol über $CaCl_2$ getrocknet und dann abgesaugt. Es blieben 2 g cis-4-N-*Phenylamino-cyclopenten*-(2)-*ol*-(1) (VI) zurück. VI wurde mit Natriumacetat und Acetanhydrid 1 Stunde auf 120° erwärmt. Dann wurde mit verd. Natronlauge neutralisiert und der Niederschlag aus Petroläther umkristallisiert; das *Diacetat* VII hat F.102–103° (Gef. C, 70·09; H, 6·87; N, 5·83. $C_{15}H_{17}NO_3$ erfordert; C, 69·48; H, 6·62; N, 5·40).

VII gibt bei Hydrierung in Gegenwart von Pt-Kohle in Cyclohexan das gesättigte Diacetat VIII.

N-*Phenyl*-2-*oxa*-4-*azabicyclo*-[3.2.1]-*octan* (IX)

3 g V wurden mit 15 ml Formalin vermischt und 1 Stunde auf 60° erwärmt. Die Mischung wurde dann mit 30 ml Äther ausgeschüttelt, der Äther mit Wasser gewaschen, über $CaCl_2$ getrocknet und abgesaugt. Der Rückstand wurde destilliert: 2 g IX, $Kp_{0·5}$ 107–110° (Gef. C, 75·69; H, 8·08; N, 7·83; $C_{12}H_{15}NO$ erfordert: C, 76·16, H, 7·99, N, 7·40%).

N-*Phenyl*-2-*oxa*-3-*azabicyclo*-[3.2.2]-*nonadien*-(5.x) (XII)

5 g Nitrosobenzol wurden in 50 ml Äther gelöst, zu der auf 0° gekühlten Lösung wurden 6 g Cycloheptatrien zugefügt (Molverhältnis 1:1·4). Im Verlaufe einer Woche färbte sich die Lösung dunkel. Nach 14 Tagen wurde der Äther abgesaugt, der Rückstand durch Wasserdampfdestillation von unumgesetzten Nitrosobenzol und Cycloheptatrien befreit und dann mit 50 ml Äther ausgeschüttelt. Der Äther wurde über $CaCl_2$ getrocknet, abgesaugt und der dunkle Rückstand mit Benzol an Al_2O_3 chromatographiert. Es wurden 1·5 g (20% d.Th.) XII, farblose Kristalle mit F.107–108°, erhalten. (Gef. C, 78·23; H, 6·60; N, 6·85; $C_{13}H_{13}NO$ erfordert: C, 78·37; H, 6·57; N, 7·03%).

N-*Phenyl*-2-*oxa*-3-*azabicyclo*-[3.2.2]-*nonan* (XIII)

(*a*) 2 g XII wurden in 20 ml Cyclohexan gelöst und in Gegenwart von 0·5 g Platin-Kohle bei Raumtemperatur und Atmosphärendruck hydriert. Es wurden 580 ml H_2 aufgenommen (berechnet für 2 Doppelbindungen 450 ml). Der Katalysator wurde abfiltriert und mit Methanol ausgewaschen, die Lösungsmittel wurden abgesaugt. Es blieben 2 g eines gelblichen Öles zurück, das in Petroläther bei −10° kristallisierte. XIII hat F.27–28° (Gef. C, 77·41; H, 8·47; N, 6·89; $C_{13}H_{17}NO$ erfordert: C, 76·80; H, 8·45; N, 6·89%).

(*b*) 1 g von XII wurde in 10 ml Cyclohexan gelöst und mit Raney-Nickel bei Raumtemperatur und Atmosphärendruck hydriert. Es wurden 236 ml H_2 aufgenommen (berechnet 224 ml). Der Katalysator wurde abfiltriert und mit Methanol ausgewaschen, die Lösungsmittel wurden abgesaugt, der Rückstand wurde mit Benzol an Al_2O_3 chromatographiert. Es wurden 2 Fraktionen aufgefangen. Die erste Fraktion blieb nach dem Absaugen des Lösungsmittels flüssig, ihr IR-Spektrum war mit dem Spektrum von XIII identisch. Nach dem Absaugen des Benzols der 2.Fraktion blieb eine geringe Menge Substanz zurück, die beim Anreiben mit Äther kristallisierte. Sie hatte den Schmelzpunkt F.54–56°, ihr IR-Spektrum war mit dem von XIV identisch.

cis-4-N-*Phenylamino-cycloheptanol* (XIV)

1 g XIII wurden in 15 ml Eisessig gelöst und mit 3 g Zinkpulver reduziert. Nach 2 Stunden wurde die Lösung mit 15 g NaOH in 30 ml Wasser alkalisch gemacht und einer Wasserdampfdestillation unterworfen. Das Wasser-Zinkoxyd-Gemisch wurde filtriert, der Rückstand mit 30 ml warmem

Benzol ausgewaschen und das Filtrat mit dem Benzol ausgeschüttelt. Das Benzol wurde über $CaCl_2$ getrocknet und dann abgesaugt. Der Rückstand kristallisierte mit Äther-Petroläther. Die Kristalle, bei denen es sich um ein Ätherat handeln muss, schmolzen zwischen 55 und 60°. Bewahrt man sie einige Zeit im Vakuum auf, so verflüssigen sie sich wieder. Eine Probe wurde 48 Stunden im Vakuum aufbewahrt und dann analysiert. (Gef. C, 75·26; H, 9·05; N, 7·01; $C_{13}H_{19}NO$ erfordert: C, 76·05; H, 9·34; N, 6·83%).

cis-4-N-*Phenylaminocycloheptadienol* (XV)

1 g XII wurde in 15 ml Eisessig gelöst und mit 3 g Zinkpulver reduziert. Nach 2 Stunden wurde die Lösung mit 15 g NaOH in 30 ml Wasser alkalisch gemacht, filtriert, der Rückstand mit 50 ml Äther ausgewaschen und das Filtrat mit Äther ausgeschüttelt. Der Äther wurde über $CaCl_2$ getrocknet und dann abgesaugt, der Rückstand erstarrte beim Reiben allmählich. Aus Petroläther umkristallisiert, hatte XV den F.64–65·5° (Gef. C, 78·07; H, 7·63; N, 7·05; $C_{13}H_{15}NO$ erfordert: C, 77·58; H, 7·52; N, 6·96%).

Wir danken dem Fonds der chemischen Industrie für die Unterstützung dieser Arbeit.

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THE REARRANGEMENT OF 4,5,6,7-TETRACHLORO-3a,4,7,7a-TETRAHYDRO-4,7-METHANOIDEN-8-ONE[1]

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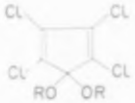
(*Received* 2 *August* 1960)

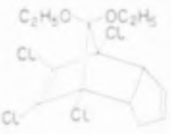
Abstract—4,5,6,7-Tetrachloro-3a,4,7,7a-tetrahydro-4,7-methanoinden-8-one (IV) has been prepared by the hydrolysis of the adduct of cyclopentadiene and 1,2,3,4-tetrachloro-5,5-diethoxycyclopentadiene. It has been shown to undergo quantitative thermal isomerization to 2,3, 3a, 7a-tetrachloro-3a, 4,7,7a-tetrahydro-4,7-methanoinden-1-one (XV), whose structure has been established by its degradation to 2,3-dichloro-bicyclo[2.2.1] heptane-2,3-dicarboxylic acid anhydride (XXI). Aluminum chloride has been found to exercise a remarkably strong accelerating effect on the isomerization reaction. The pathway of the isomerization reaction is interpreted in terms of views recently advanced by Woodward and Katz. Stereochemical assignments are suggested and are corroborated, in part, by the observation that XV undergoes photoisomerization to give a cage compound (XXXI).

THE Diels–Alder reaction of 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene (I) and its diethoxy analogue (II) with dienophiles is well-known[3] and provides a convenient route for the preparation of bicyclo[2.2.1]hepten-7-one derivatives.[3b] The work here described is concerned with the preparation and isomerization of the ketone of this type derived from the adduct of II[4] and cyclopentadiene.

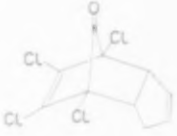


I, R = CH_3

II, R = C_2H_5



III



IV

The major product obtained in the reaction of cyclopentadiene with II was a 1:1 adduct[5] which is assigned structure III on the basis of its mode of formation, infrared spectrum, and conversion to the corresponding ketone, 4,5,6,7-tetrachloro-3a,4,7,7a-tetrahydro-4,7-methanoinden-8-one (IV), on treatment with concentrated sulfuric acid. The assignment of structure IV to the hydrolysis product is based on its infrared

[1] Part of this work has been treated in a preliminary report: P. Yates and P. Eaton, *Tetrahedron Letters* No. 11, 5 (1960).

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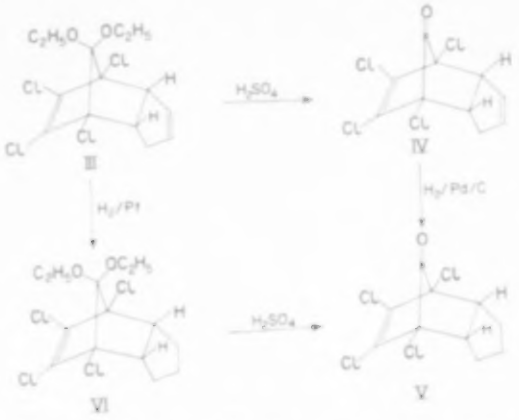
[3a] J. S. Newcomer and E. T. McBee, *J. Amer. Chem. Soc.* **71**, 946 (1949); J. W. Dawson and W. J. Croxall, U.S. Pat. 2,562,893 (1951); cf. *Chem. Abstr.* **46**, 1587 (1952); [b] E. T. McBee, W. R. Diveley and J. E. Burch, *J. Amer. Chem. Soc.* **77**, 385 (1955); H. E. Ungnade and E. T. McBee, *Chem. Rev.* **58**, 249 (1958); [c] C. A. Peri, *Gazz. Chim. Ital.* **85**, 1118 (1955).

[4] J. A. Krynitsky and R. W. Bost, *J. Amer. Chem. Soc.* **69**, 1918 (1947).

[5] This product has been obtained previously by Peri[3c] and by E. P. Ordas, U.S. Pat. 2,697,103 (1954), cf. *Chem. Abstr.* **49**, 15956 (1955).

spectrum, which shows bands at 3·34, 5·48 and 6·33 μ, attributable to vinylic hydrogen, carbonyl, and ethylenic stretching vibrations, respectively. The unusually low wave length of the carbonyl band is characteristic of the bridge carbonyl group of polychlorobicyclo[2.2.1]heptan-7-one systems,[6,7] while the unusually high wave length of the ethylenic double bond stretching band is characteristic of *cis*-1,2-dichloroethylenic systems.[6,8] On hydrogenation over palladium-charcoal in methanol IV was converted to the dihydro compound V, whose infrared spectrum also shows bands at 5·48 and 6·33 μ, but lacks the vinylic hydrogen band of IV at 3·34 μ.



Attempts to hydrolyse the ketal III under milder conditions were unsuccessful; thus, it was recovered unchanged after treatment with 80 per cent sulfuric acid at room temperature.[9] Because of the severity of the conditions under which IV was formed it was considered possible that the reaction might have proceeded with rearrangement, and that the ketone might not be so simply related to its precursor as represented by the expressions III and IV. This relationship was confirmed, however, by the preparation of the dihydro compound VI from III by hydrogenation over platinum in methanol, and the hydrolysis of this product to a ketone identical in all respects to V, the product obtained by hydrogenation of IV. The *endo*-configuration is assigned to the adduct III by analogy;[10] the *endo* configurations for its transformation products IV–VI then follow.

When the adduct III was heated with 1,2,3,4-tetrachloro-5,5-diethoxycyclopentadiene (II) in boiling xylene a second Diels–Alder reaction occurred giving a bis-adduct.

[6] E. T. McBee, D. K. Smith and H. E. Ungnade, *J. Amer. Chem. Soc.* **77**, 559 (1955).

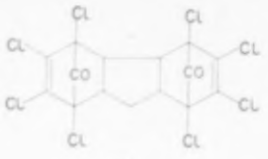
[7] This shift must be due to both the angle deformation (J. O. Halford, *J. Chem. Phys.* **24**, 830 (1956)) at this carbonyl group (cf. Ref. 9) and the presence of the electronegative chlorine atoms; thus, in the absence of the latter, the bridge carbonyl band occurs at ca. 5·6 μ; cf. for example, P. Wilder, Jr. and A. Winston, *J. Amer. Chem. Soc.* **78**, 868 (1956); C. H. DePuy and B. W. Ponder, *Ibid.* **81**, 4629 (1959).

[8] Cf. the ethylenic stretching band of *cis*-1,2-dichloroethylene itself, which falls at 6·29 μ: T.-Y. Wu, *Phys. Rev.* **46**, 465 (1934).

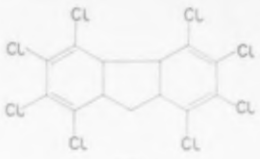
[9] The need for more stringent conditions must reflect the difficulty of converting the single carbon bridge atom from its sp^3 hybridization state in III to the sp^2 hybridization state in the grouping $>C{=}\overset{\oplus}{O}C_2H_5 \leftrightarrow >\overset{\oplus}{C}{-}OC_2H_5$, engendered by the abnormally small C—C—C bond angle at this carbon atom (cf. W. G. Woods, R. A. Carboni and J. D. Roberts, *J. Amer. Chem. Soc.* **78**, 5653 (1956)).

[10] M. C. Kloetzel, *Organic Reactions* Vol. IV, p. 11. John Wiley, New York (1948); K. Alder and M. Schumacher, *Fortschr. Chem. Naturstoffe* **10**, 17 (1953).

This was converted by concentrated sulfuric acid to a diketone, formulated as VII on the following grounds. Its infrared spectrum, with bands at 5·49 and 6·35 μ, is in

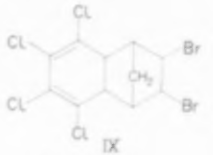


VII

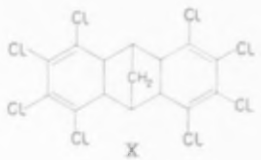


VIII

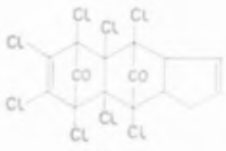
accord with the postulated structure, but excludes the possibility that the second Diels–Alder reaction is preceded by rearrangement of III (*vide infra*). When pyrolyzed at 210° it lost carbon monoxide and gave a product, $C_{13}H_6Cl_8$, which can be formulated as VIII on the basis of the relationship of its ultraviolet spectrum (see Experimental) to that of IX and of X;[11] this result permits the rejection of the alternative formulation XI for the diketone. The assignment of structure VII to the diketone leads to the assignment of structure XII to the bis-adduct itself.[12]



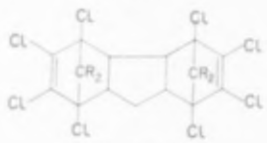
IX



X



XI



XII (R = OC_2H_5)

In contrast to the usual behaviour of bicyclo[2,2,1]hepten-7-one derivatives,[3b,11,13] the ketone IV did not lose carbon monoxide on being heated at 135° for one hour but was converted in quantitative yield to an isomer. The infrared spectrum of the rearrangement product, with bands at 3·23, 5·73 and 6·30 μ, shows that, while the *cis*-1,2-dichloroethylenic system is probably retained, the carbonyl group is no longer at the single carbon bridge of a bicyclo[2,2,1]heptene system. Its ultraviolet spectrum, λ_{max}^{EtOH} 255 mμ (ε 9100), indicates the presence of a conjugated ketonic carbonyl group. On the basis of these spectral data structure XV is assigned to the isomer; they may be compared with those of XIII,[6] $\lambda_{max}^{CCl_4}$ 5·75 and 6·39 μ, λ_{max}^{EtOH} 258 mμ (ε 9000), and of XIV,[14] $\lambda_{max}^{CCl_4}$ 5·70, 6·17 and 6·34 μ, λ_{max}^{EtOH} 258 mμ (ε 6700).

Confirmation of this structural assignment was obtained in the following way. Hydrogenation of XV over platinum in methanol gave a dihydro compound, XVI, with infrared bands at 5·74 and 6·30 μ, but lacking the vinylic hydrogen band of XV at 3·23 μ. This product was highly resistant to oxidation, failing to react with ozone,

[11] K. MacKenzie, *J. Chem. Soc.* 473 (1960).

[12] Bis-adducts of I and II with butadiene, furan and thiophene have been obtained previously by Peri[3c], who formulated them as analogues of XII without supporting evidence. Very recently the addition of I to cyclopentene has been described.[11]

[13] C. F. H. Allen, *Chem. Rev.* 37, 209 (1945).

[14] A. Roedig and L. Hörnig, *Liebigs Ann.* 598, 208 (1956).

XIII XIV

potassium permanganate or alkaline hydrogen peroxide. On treatment with sodium methoxide in methanol it gave in high yield a product in which one of the chlorine atoms of XVI had been replaced by a methoxyl group. This product is formulated as XVII on the basis of the spectral data: infrared bands at 5·78, 6·24 and 7·73 μ,[15a] ultraviolet maximum at 264 mμ (ε 13,000).[15b] It could also be formed from XV by

reaction first with sodium methoxide in methanol to give XVIII, followed by hydrogenation. Cleavage of the enol ether XVII was effected with hydrogen bromide in acetic acid giving the β-diketone XIX, with bands in its infrared spectrum at 3·80, 4·05, 5·91 and 6·34 (very broad) μ.[16] Oxidation of this product with fuming nitric acid

[15a] Cf. the infrared spectrum of 2,3-dimethoxy-2-cyclopentenone which has bands at 5·86, 6·11 and 7·46 μ [P. Yates and C. D. Anderson, unpublished].

[15b] Thus, enol methyl ethers from 2,4- and 4,4-dimethyl-1,3-cyclopentanedione have λ_{max}^{MeOH} 242·5 mμ (ε 12,700) and 237 mμ (ε 14,500), respectively, [B. Eistert and W. Reiss, *Chem. Ber.* **87**, 108 (1954)], and it has been observed in related β-diketonic systems that substitution by halogen atoms on any of the carbon atoms adjacent to the carbonyl groups brings about appreciable, and cumulative, bathochromic shifts, provided that enolization is still possible [E. R. Blout, V. W. Eager and D. C. Silverman, *J. Amer. Chem. Soc.* **68**, 566 (1946)].

[16] Cf. the infrared spectrum of 1,3-cyclopentanedione which has bands at ca. 6·0 and 6·35 (broad) μ [J. H. Boothe, R. G. Wilkinson, S. Kushner and J. H. Williams, *J. Amer. Chem. Soc.* **75**, 1732 (1953)].

at 90° for five minutes gave an acidic product, $C_{10}H_{10}Cl_2O_5$, with bands in its infrared spectrum at 2·92, 3·4 (very broad), 5·62 and 5·75 μ; this is formulated as the lactol XX. Further oxidation with aqueous basic potassium permanganate gave XXI which was shown to be identical with the product obtained by hydrogenation of XXII, the Diels–Alder adduct from cyclopentadiene and dichloromaleic anhydride.[17] Although the stereochemistry of XVIII has not been established independently, it may be assigned the *endo* configuration with a high degree of certainty;[10] this leads to the *endo* assignment for the other members of this series, including XV. Corroboration of this configurational assignment for XV was obtained by photochemical cyclization (*vide infra*).

The facile thermal isomerization of IV to XV is reminiscent of the rearrangement of the alcohols XXIII and XXIV recently discovered by Woodward and Katz.[18] On being heated at 140° these were converted to their isomers, XXV and XXVI, respectively; in the case of the former an equilibrium mixture of XXIII and XXV was obtained, while in the latter case, although an equilibrium was undoubtedly involved, conversion of XXIV to XXVI was essentially complete. Although these investigators

XXVII XXVIII

XXIII, $R_1 = R_2 = R_3 = H$, $R_4 = OH$

XXIV, $R_1 = R_2 = R_4 = H$, $R_3 = OH$

XXV, $R_1 = OH, R_2 = R_3 = R_4 = H$

XXVI, $R_2 = OH, R_1 = R_3 = R_4 = H$

did not observe directly the isomerization of the corresponding ketones in this series, their observation that the alcohol XXV when subjected to Oppenauer oxidation with aluminum t-butoxide and quinone in boiling benzene gave the rearranged ketone XXVII was interpreted in terms of initial oxidation to the ketone XXVIII followed by facile and complete rearrangement to XXVII.[19,20] On the basis of their elegant demonstration of the retention of complete stereochemical integrity in the rearrangement of XXIII and XXIV, Woodward and Katz[18] concluded that the isomerizations proceed not by complete dissociation and recombination but, rather, by the cleavage of *one* of the bonds of the dicyclopentadiene system and the formation of a new bond via a stage XXIX. Although we lack in the case of the isomerization of IV the rigorous stereochemical arguments developed in the cases of the isomerization of XXIII and XXIV, we consider that the facility of the reaction, the absence of other

[17] A. M. Clifford and C. E. Gleim, U.S. Pat. 2,391,226 (1945); cf. *Chem. Abstr.* **40**, 3136 (1946).

[18] R. B. Woodward and T. J. Katz, *Tetrahedron* **5**, 70 (1959); as pointed out by these authors, this type of reaction is a special case of the Cope rearrangement, cf. E. G. Foster, A. C. Cope and F. Daniels, *J. Amer. Chem. Soc.* **69**, 1893 (1947).

[19] T. J. Katz, Ph. D. Thesis, Harvard (1959).

[20] This interpretation was based on the fact that the alcohol XXV failed to rearrange when heated in boiling benzene alone. However, the possibility that the rearrangement of XXV is catalysed by aluminum t-butoxide (*vide infra*) and precedes oxidation cannot be excluded. *Note added in proof:* R. C. Cookson, J. Hirdec and R. O. Williams, *Tetrahedron Letters* No. 22, 29 (1960), have very recently reported that oxidation of XXV in basic medium affords XXVIII.

products, and the inherent similarity to the earlier cases make it highly probable that the reaction proceeds by an analogous route, via XXX. The presence of the carbonyl group will undoubtedly lead to an unusually large polarization of the electronic displacements in the sense of XXXa. The observations that IV was completely converted to XV and that no detectable isomerization occurred in the reverse direction are in accord with expectation since the equilibrium IV $\rightleftharpoons$ XV should lie heavily in favor of XV, in which the carbonyl group is directly conjugated and lacks much of the disabling angle deformation peculiar to the bridge carbonyl group of IV.[7,9,21]

It was of considerable interest to find that the conversion of IV to XV took place

XXIX XXX XXX a

very rapidly at *room temperature* when a solution of IV in carbon tetrachloride was *treated with aluminium chloride*, in fact, when a large excess of this reagent was used, rearrangement was complete *within three minutes*. Acceleration of the rearrangement by aluminum chloride could also be effected in homogeneous medium by the use of a solution of aluminum chloride in dichloromethane.[22] Similar, but less striking, acceleration was brought about by ferric chloride and by sulfuric acid.[23] The action of these acidic reagents must be related to their ability to coordinate with the carbonyl oxygen atom of IV and thus to facilitate the bond-breaking process symbolized in XXX and XXXa. It may be noted that catalysis of the Diels–Alder reaction by acids has been observed in several instances.[24] This common feature of the Diels–Alder reaction and of the rearrangement here discussed is of interest in the light of the postulated relationship between these two types of reaction.[18] We have been led thereby to the exploration of the efficacy of aluminum chloride in the acceleration of the Diels–Alder reaction; preliminary results indicate that in some cases this reagent serves this purpose in excellent fashion.[25]

We turn finally to some photochemical experiments which shed further light on the stereochemistry of XV. When this compound in solution in carbon tetrachloride was irradiated overnight with a water-cooled Hanovia 450 watt mercury arc source, it was converted in part to a *new isomer*, whose infrared spectrum shows a band at 5·52 μ but lacks the bands of XV at 3·23, 5·73 and 6·30 μ. Its ultraviolet spectrum, unlike that of XV, shows no high intensity absorption, but a weak plateau at ca. 295 mμ (ε 30) and weak end absorption (ε_{210} 630). These spectral data clearly indicate that the photoproduct contains neither vinylic hydrogen atoms nor a *cis*-1,2-dichloroethylenic

[21] A similar situation clearly holds in the case of the equilibrium XXVII $\rightleftharpoons$ XXVIII.[19]

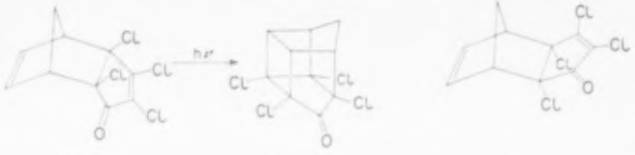
[22] This result eliminates the possibility that the acceleration of the isomerization depends on an interaction with the aluminum chloride surface.

[23] In the latter case a two-phase system, consisting of sulfuric acid and a solution of IV in carbon tetrachloride was used; this system differed from that used for the preparation of IV by the action of sulfuric acid on III, when no solvent was used. Some rearrangement of IV to XV occurred under these conditions also, however XV was not observed in the product isolated since it, unlike IV, is soluble in sulfuric acid.

[24] W. Rubin, H. Steiner and A. Wassermann, *J. Chem. Soc.* 3046 (1949), and earlier papers; A. Rodgman and G. F. Wright, *J. Org. Chem.* **18**, 465 (1953); L. E. Gast, E. W. Bell and H. M. Teeter, *J. Amer. Oil Chemists Soc.* **33**, 278 (1956).

[25] P. Yates and P. Eaton, *J. Amer. Chem. Soc.* **82**, 4436 (1960).

system and that its carbonyl group occupies a highly strained position and is no longer conjugated. This isomer is therefore assigned the structure XXXI.[26] Such a cage compound can arise only from the *endo* compound XV, and not from its *exo*-stereoisomer, XXXII. The possibility that XXXI was directly derived not from XV, but from IV, formed by initial isomerization of XV under the influence of the ultraviolet



XV XXXI XXXII

radiation (i.e. by reversal of the thermal isomerization process IV → XV) is excluded by the observation that IV was unaffected by such irradiation. Thus, the earlier assignment of the *endo* configuration to the thermal isomerization product, XV, is corroborated by the photochemical experiments.[27] Further, it may be noted that the Woodward–Katz mechanism requires that XV be formed from the *endo* isomer IV, rather than its *exo* analogue, and hence the earlier postulation of *endo* configurations for III and its congeners is consistent with the views subsequently developed.

EXPERIMENTAL[28]

1,2,3,4-*Tetrachloro*-5,5-*diethoxycyclopentadiene* (II)

A freshly prepared ethanolic solution of sodium ethoxide (from 93 g sodium in 1800 ml absolute ethanol) was added slowly with stirring to a solution of hexachlorocyclopentadiene (500 g) in absolute ethanol (1 l.). During the addition the solution temp was maintained at 30–35° by external cooling. After being stirred overnight, the solution was diluted with water (2 l.) and carbon tetrachloride (300 ml) was added to decrease the viscosity of the oil which separated. The organic layer was separated and washed with water, followed by 1% hydrochloric acid until the wash liquids were slightly acid. The organic residue was fractionated *in vacuo* to give 417 g (78%) of a greenish-yellow, sweet-smelling liquid, b.p. 124–127° 11 mm (lit[24] b.p. 101–103° 5 mm).

4,5,6,7-*Tetrachloro*-8,8-*diethoxy*-3a,4,7,7a-*tetrahydro*-4,7-*methanoindene* (III)

Freshly distilled cyclopentadiene (103 g) was added to II (400 g) in purified hexane (340 ml). A few crystals of hydroquinone were added as a polymerization inhibitor. After the initial exothermic reaction subsided, the solution was boiled under reflux overnight. Distillation through an efficient fractionation column at a 5:1 reflux ratio gave 407 g of slightly yellow liquid, b.p. 100–109° 0·1 mm. This material crystallized from methanol as fine, white needles (398 g, 81%), m.p. 54–55° (lit[26] m.p. 49–50°); λ_{max} 3·23, 3·32, 3·40, 6·22, 8·48 μ. (Found: C, 47·22; H, 4·28; Cl, 39·38. Calc. for $C_{14}H_{16}Cl_4O_2$: C, 46·95; H, 4·50; Cl, 39·61%).

4,5,6,7-*Tetrachloro*-3a,4,7,7a-*tetrahydro*-4,7-*methanoinden*-8-*one* (IV)

Three hundred grams III were added as a melt to conc sulfuric acid (200 ml) with vigorous agitation. After being stirred for 24 hr, the mixture was filtered through a sintered glass funnel. The brown granular residue was pulverized with chipped ice (100 g). The resulting tan powder was taken up in pet ether; this solution was washed with water, dried, and decolorized with activated charcoal. Five crops of crystals (total, 120 g, 48%) were obtained by repeated concentration of this solution.

[26] Cf. the related photoisomerization reactions observed by R. C. Cookson, E. Crundwell and J. Hudec, *Chem. & Ind.* 1003 (1958).

[27] This argument lacks complete rigor in that it is possible, albeit unlikely, that XXXI might have been derived indirectly from the *exo* isomer XXXII by its initial photoisomerization to the *endo* isomer XV via complete dissociation and recombination.

[28] Melting points are uncorrected. Carbon tetrachloride was used as the solvent for infrared spectral determinations, unless otherwise noted. Petroleum ether refers to a fraction with b.p. 30–60°.

The fine, white needles had m.p. 123–123·5°; λ_{max} 3·34, 3·40, 3·48, 5·48, 6·33 μ; λ_{max}^{EtOH} 260 mμ (shoulder, ϵ 190). (Found: C, 42·32; H, 2·05; Cl, 49·86; M.W., 250. Calc. for $C_{10}H_6Cl_4O$: C, 42·29; H, 2·13; Cl, 49·94%; M.W. 284).

4,5,6,7-*Tetrachloro*-8,8-*diethoxy*-2,3,3a,4,7,7a-*hexahydro*-4,7-*methanoindene* (VI)

A solution of III (5 g, 0·014 mole) in 50 ml methanol was treated with hydrogen at 1 atm over platinum. Hydrogen uptake ceased after the absorption of one molar equivalent. The catalyst was filtered and the solution partially evaporated to give 4·2 g (83%) of the dihydro derivative (VI). Recrystallization from methanol gave colorless crystals, m.p. 76–76·5°; λ_{max} 3·34, 3·42, 6·22, 8·48 μ (Found: C, 46·89; H, 4·76. Calc. for $C_{14}H_{18}Cl_4O_2$: C, 46·69; H, 5·04%).

4,5,6,7-*Tetrachloro*-2,3,3a,4,7,7a-*hexahydro*-4,7-*methanoinden*-8-*one* (V)

(i) *From hydrolysis of* VI. Two grams VI were shaken with conc sulfuric acid (20 ml) for 15 min. The mixture was then poured onto cracked ice. The resultant solid was filtered and twice crystallized from pet ether, giving V as white crystals (0·9 g, 56·5%), m.p. 68·5–69·5°; λ_{max} 3·40, 3·48, 5·48, 6·33 μ. (Found: C, 41·97; H, 3·10. Calc. for $C_{10}H_6Cl_4O$: C, 41·99; H, 2·82%).

(ii) *From hydrogenation of* IV. A solution of IV (2 g, 0·0073 mole) in methanol (30 ml) was treated with hydrogen at atm press over palladium/charcoal. Hydrogen uptake ceased after the absorption of one molar equivalent. The catalyst was filtered and the solution diluted with water (150 ml). The oil which separated was taken up in pet ether. The solution was dried, decolorized, and concentrated to give 1·8 g (89·5%) of a crystalline product identical to the ketone obtained by hydrolysis of VI. A mixture m.p. of the two products showed no depression; their infra-red spectra were identical.

1,2,3,4,5,6,7,8-*Octachloro*-1,4,4a,4b,5,8,8a,9a-*octahydro*-1, 4:5,8-*dimethano-fluoren*-10,11-*dione* (VII)

A solution of III (3·58 g, 0·01 mole) and 1,2,3,4-tetrachloro-5,5-diethoxycyclopentadiene (5 g, 0·017 mole) in xylene (40 ml) containing a few crystals of hydroquinone was boiled under reflux overnight. When the solution was cooled, 6·3 g (97%) of adduct crystallized. Four grams of this product were stirred vigorously with conc sulfuric acid (30 ml) for 6 hr. Dilution of the solution with ice-water precipitated the diketone VII. Repeated crystallization of the crude product from large volumes of carbon tetrachloride gave 2·6 g (84%) of glistening white plates, m.p. 200° (with evolution of carbon monoxide); λ_{max}^{KBr} 5·49, 6·35 μ.

(Found: C, 35·85; H, 1·45; Cl, 57·08. Calc. for $C_{13}Cl_8H_6O_2$: C, 35·90; H, 1·21; Cl, 56·52%).

1,2,3,4,5,6,7,8-*Octachloro*-4a,4b,8a,9a-*tetrahydrofluorene* (VIII)

One gram of the diketone VII was heated in a test tube maintained at 210° by a bath of refluxing nitrobenzene until carbon monoxide evolution ceased (ca. 10 min). The residue crystallized from hot carbon tetrachloride as white needles, m.p. 207–208°; λ_{max} 6·48 μ; $\lambda_{max}^{Et_2O}$ 263 mμ (shoulder, ϵ 9200), 273 mμ (ϵ 11,200), 284 mμ (ϵ 12,800), 295 mμ (ϵ 11,800), 308 mμ (ϵ 7400).

(Found: C, 35·34; H, 1·49; Cl, 63·33. Calc. for $C_{12}Cl_8H_6$: C, 35·02; H, 1·36; Cl, 63·62%).

Thermal isomerization of IV: *Formation of* 2,3,3a,7a-*tetrachloro*-3a,4,7,7a-*tetrahydro*-4,7-*methanoinden*-1-*one* (XV)

Two hundred grams IV were heated at 135° for 1 hr. On solidification of the melt a quantitative yield of the rearranged ketone (XV) was obtained. Crystallization from ligroin (b.p. 66–75°) gave large, colorless crystals, m.p. 82–83°; λ_{max} 3·23, 3·31, 3·44, 5·73, 6·30 μ; λ_{max}^{EtOH} 255 mμ (ϵ 9100).

(Found: C, 42·53; H, 2·14; Cl, 49·86; M.W., 288. Calc. for $C_{10}H_6Cl_4O$: C, 42·29; H, 2·13; Cl, 49·94%; M.W., 284).

An infrared spectrum of a concentrated solution of the material prior to crystallization showed no band at 5·48 μ, indicating the absence of unreacted IV and the Diels–Alder dimer of tetrachlorocyclopentadienone. The completeness and unidirection of the thermal rearrangement process was further demonstrated by the heating of a small sample of pure IV in a m. p. capillary tube at 135° for 5 min; after cooling and subsequent solidification, the sample had m.p. 82–83°, identical to the m.p. of pure XV.

2,3,3a,7a-*Tetrachloro*-3a,4,5,6,7,7a-*hexahydro*-4,7-*methanoinden*-1-*one* (XVI)

A solution of XV (50 g, 0·176 mole) in warm methanol (300 ml) was treated with hydrogen at atm press over platinum. Hydrogen uptake was very rapid and stopped sharply after the absorption of one molar equivalent. The catalyst was filtered and water (600 ml) was added. The oil which separated was taken up in ether; the solution was dried, decolorized, and diluted with pet ether. Two crops of white crystals were obtained by concentration of this solution. Recrystallization from pet ether gave 44 g (87%) of the dihydro compound XVI, m.p. 65–65·5°; λ_{max} 3·35, 3·45, 5·74, 6·30 μ.

(Found: C, 42·11; H, 3·04. Calc. for $C_{10}H_8Cl_4O$: C, 41·99; H, 2·82%).

2,3a,7a-*Trichloro*-3-*methoxy*-3a,4,5,6,7,7a-*hexahydro*-4,7-*methanoinden*-1-*one* (XVII)

(i) *From* XVI. Freshly prepared methanolic sodium methoxide (from 4·05 g sodium in 50 ml methanol) was added rapidly with stirring to a solution of XVI (40 g) in methanol (300 ml). Sodium chloride was precipitated almost immediately. After 15 min, water (600 ml) was added. The resulting precipitate was crystallized from hot methanol to give a virtually quantitative yield (39·2 g) of white crystals, m.p. 102·5–103·5°; λ_{max} 3·35, 3·45, 5·78, 6·24, 7·73 μ; λ_{max}^{EtOH} 264 mμ (ε 13,000).

(Found: C, 47·12; H, 3·93. Calc. for $C_{11}H_{11}Cl_3O_2$: C, 46·92; H, 3·94%).

(ii) *From hydrogenation of* XVIII. A solution of XVIII (1 g, 0·00358 mole) in methanol (30 ml) was treated with hydrogen at 1 atm over platinum. Hydrogen uptake ceased after the absorption of one molar equivalent. The catalyst was filtered. On concentration the filtrate deposited 0·9 g (88·5%) of crystalline material identical to the product obtained by the action of sodium methoxide on XVI. A mixture m.p. of the two products showed no depression, their infrared spectra were identical.

2,3a,7a-*Trichloro*-3-*methoxy*-3a,4,7,7a-*tetrahydro*-4,7-*methanoinden*-1-*one* (XVIII)

This compound was prepared from XV (0·5 g) and sodium methoxide by the same procedure as that used for the preparation of XVII from XVI. Crystallization of the product from methanol gave a quantitative yield of white plates, m.p. 106–106·5°; λ_{max} 3·30, 3·38, 3·44, 5·82, 6·25, 7·73 μ.

(Found: C, 47·57; H, 3·20; Cl, 37·91. Calc. for $C_{11}H_9Cl_3O_2$: C, 47·26; H, 3·25; Cl, 38·05%).

2,3a,7a-*Trichloro*-3a,4,5,6,7,7a-*hexahydro*-4,7-*methanoinden*-1,3-*dione* (XIX)

A solution of XVII (25 g) in glacial acetic acid (100 ml) and a 30–35% solution of hydrogen bromide in acetic acid (25 g) were heated together on the steam-bath for 4 hr. The container was sealed except for a fine capillary for pressure release. As the reaction proceeded large, tan crystals separated. These were recrystallized from methanol to give 20·4 g (86%) of colorless crystals, m.p. 233° dec; λ_{max}^{KBr} 3·35, 3·80, 4·05, 5·91, 6·34 (v. broad) μ.

(Found: C, 44·83; H, 3·27; Cl, 39·80. Calc. for $C_{10}H_9Cl_3O_2$: C, 44·89; H, 3·39; Cl, 39·76%).

Oxidation of XIX *with nitric acid: Formation of* XX

Ten grams of XIX in a 50 ml round-bottomed flask equipped with a condenser were covered with fuming nitric acid (85%, 30 ml). A vigorous reaction ensued and brown fumes were evolved immediately. Complete reaction was effected by heating the flask on the steam-bath until no further evolution of brown fumes was evident. The solution on cooling in an ice-salt bath deposited fine, white needles. These were freed of nitric acid and dried by prolonged treatment with boiling benzene under a Dean–Stark trap. Dilution of the benzene solution with ligroin (b.p. 100–105°) and concentration gave 5·2 g (50%) of large, colorless cubic crystals of XX, dec 200°; λ_{max}^{KBr} 2·92, 3·4 (v. broad), 5·62, 5·75 μ.

(Found: C, 42·69; H, 3·69; Cl, 24·68; N.E., 140. Calc. for $C_{10}H_{10}Cl_2O_5$: C, 42·73; H, 3·59; Cl, 25·23%; N.E., 140·5).

2,3-*Dichlorobicyclo*[2,2,1]*heptane*-2,3-*dicarboxylic acid anhydride* (XXI)

(i) *From alkaline permanganate oxidation of* XX. One gram XX was dissolved in distilled water (6 ml) by the addition of sufficient sodium carbonate to maintain the pH at 10. Aqueous potassium permanganate (0·9 g in 20 ml water) was added slowly over $\frac{1}{2}$ hr with constant stirring. After 3 additional hr, the solution was bleached and the precipitated manganese dioxide dissolved by the addition of conc hydrochloric acid and sulfur dioxide. The solution was saturated with ammonium sulfate and extracted with ether. The extract was evaporated to dryness in a sublimation tube; the

tube was then evacuated and heated gently. The colorless sublimate thus obtained was recrystallized from ether to give 7·2 g (87%) of XXI, m.p. 202–203° (sealed cap); λ_{max} 5·28, 5·36, 5·53 μ.

(Found: C, 46·04; H, 3·67; Cl, 29·89. Calc. for $C_9H_6Cl_2O_2$: C, 45·98; H, 3·43; Cl, 30·17%).

(ii) *From hydrogenation of* XXII. A solution of XXII (1 g, 0·0043 mole) in anhydrous ether (50 ml) was treated with hydrogen at 1 atm over platinum. Hydrogen uptake ceased after the absorption of one molar equivalent. The catalyst was filtered and the solution concentrated; white crystals (0·6 g, 59·5%) were deposited. After one sublimation *in vacuo*, these gave a product identical to the product obtained by oxidation of XX. A mixture m.p. of the two products showed no depression; their infrared spectra were identical.

Dichloromaleic anhydride[25]

A solution of mucochloric acid (100 g), in fuming nitric acid (200 ml) was boiled under reflux overnight. On cooling, the solution deposited long, white needles which were filtered and heated over an intense free flame; after removal of nitric acid and water, the product distilled readily and crystallized immediately giving 85 g (86·5%) of flaky, white crystals, m.p. 119–120° (lit[25] m.p. 119–120°); λ_{max} 5·40, 5·50, 5·60, 6·23, 10·8 μ.

2,3-*Dichlorobicyclo*[2,2,1]*hept*-5-*ene*-2,3-*dicarboxylic acid anhydride* (XXII)

A heavy-walled glass pressure bottle was charged with dichloromaleic anhydride (10 g) and freshly distilled cyclopentadiene (5 g), sealed, and heated under autogenous pressure at 150° for 45 min. After cooling, the resulting solid mass was ground up and extracted with a large volume of ether. Decolorization, followed by partial evaporation of the ether extract, gave 8 g (57%) of white crystals, m.p. 189–190° (sealed cap) (lit.[17] m.p. 188–189°); λ_{max} 5·31, 5·38, 5·55, 6·17 μ.

(Found: C, 46·48; H, 2·82. Calc. for $C_9H_6Cl_2O_3$: C, 46·38; H, 2·60%).

Acceleration of the isomerization of IV *to* XV *by aluminum chloride*

Aluminum chloride (0·3 g) was added to a solution of IV (0·10 g) in carbon tetrachloride (5 ml), and the mixture was swirled for 3 min. The reaction was then quenched with ice-water (50 ml). The organic layer was dried over sodium sulfate and stripped of solvent *in vacuo*. The infrared spectrum of the residue showed that complete isomerization to XV had occurred. Similar results were obtained with dichloromethane as solvent, using both heterogeneous and homogeneous systems. Marked acceleration of the isomerization was also observed when solutions of IV in carbon tetrachloride were treated with ferric chloride or concentrated sulfuric acid in large excess, but infrared spectral analysis showed that these reagents were not as effective as aluminum chloride.

2,3,5,6-*Tetrachloropentacyclo*[5.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]*decan*-4-*one* (XXXI)

A solution of XV (3 g) in carbon tetrachloride (25 ml) contained in a small quartz flask was irradiated overnight with water-cooled Hanovia 450 watt mercury arc. The solution was concentrated *in vacuo* to 6 ml and chromatographed on Davison silica with carbon tetrachloride as eluent. One gram of VI was recovered from the early eluates. Spectral analysis of intermediate fractions showed the presence of XXXI and its hydrate, while later fractions contained photodecomposition products of the solvent. Removal of solvent from the intermediate fractions followed by sublimation of the residue at 60° under high vacuum gave 1·7 g of colorless material; crystallization from dichloromethane–ligroin (b.p. 66–75°) and two sublimations gave 0·48 g (24%, based on starting material consumed) of pure product, m.p. 113·5–114·5°, λ_{max} 5·52 μ, $\lambda_{max}^{Et_2O}$ 295 mμ (plateau, ε 30), ε_{216} 630.

(Found: C, 42·09; H, 1·82; Cl, 49·76. Calc. for $C_{10}H_6Cl_4O$: C, 42·29; H, 2·13; Cl, 49·94%).

Irradiation of IV under similar conditions returned only starting material.

Acknowledgements—Part of this work was carried out during the tenure of a National Science Foundation Cooperative Fellowship by P. E. We are greatly indebted to the General Chemical Division, Allied Chemical Corporation, for a grant which defrayed the cost of this investigation.

[25] Cf. G. L. Ciamician and P. Silber, *Ber. Dtsch. Chem. Ges.* **16**, 2396 (1883).

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THE ROLE OF ACIDITY IN THE KINETICS OF AROMATIC COMPOUND NITRATION

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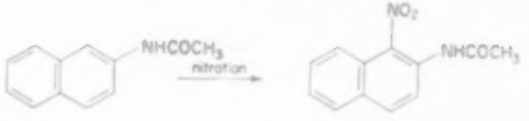
Abstract—Colorimetric method was used for investigation of the nitration rate in the solutions $HNO_3 + H_2O$, $HNO_3 + CH_3COOH + H_2O$, $HNO_3 + H_2SO_4 + H_2O$, $HNO_3 + HClO_4 + H_2O$. A mechanism of nitration of aromatic compounds based on a system of protolytic equilibria is proposed.

IN the work of Minc *et al.*[1-4]—based on the investigation of cathodic polarization and Raman spectra of nitric acid solutions—it was concluded that an increase of medium acidity* caused weakening of the HO—NO_2 bond and it was suggested that the HO—NO_2 molecule is the nitrating agent in the absence of nitronium ions (NO_2^+). This point of view is opposed to that of Ingold *et al.*[5] who state that the nitric acid molecule under similar conditions cannot be the nitrating agent. The present work is an investigation of the problem by means of nitration kinetics.

The colorimetric method used in this work enabled the concentration of a coloured nitroderivative formed during nitration to be determined. An important problem was the selection of an aromatic compound which would fulfil the following experimental requirements: (a) one-step nitration with a measurable rate in all investigated solutions, (b) a colourless compound with a coloured nitroderivative, (c) good solubility of both in the investigated solutions, (d) agreement with Lambert-Beer's law.

After preliminary experiments, N-acetyl-2-naphthylamine (ArH) was chosen. It is nitrated to the 1-nitro-N-acetyl-2-naphthylamine ($ArNO_2$)



colourless yellow

In order to determine the $ArNO_2$ concentration on the basis of extinction measured, the validity of Beer's law was tested. The Lambert-Beer's law in the form

$$\log \frac{I_0}{I} = E = \varepsilon hc$$

* Acidity is considered as a function of the strength and concentrations of all acids and bases in the solution.

[1] S. Minc, *Bull. Acad. Polon. Sci.* Cl. III, **1**, 333 (1953).
[2] S. Minc and S. Jasielski, *Roczniki Chem.* **28**, 109 (1954).
[3] S. Minc and Z. Kecki, *Roczniki Chem.* **30**, 935 (1956).
[4] S. Minc, Z. Kecki and S. Osiecki, *Bull. Acad. Polon. Sci.* Cl. III, **5**, 343 (1957).
[5] C. K. Ingold *et al. J. Chem. Soc.* 2441 (1950).

expresses the proportionality between the extinction E and concentration c only on condition that the extinction coefficient ε and the length of the absorbing path h remain constant (the latter was fulfilled in the photocolorimeter construction). The constancy of ε was tested as follows: ArH was introduced into the nitrating mixture and after completion of the reaction the solution was diluted with the same nitrating mixture in suitable proportions to obtain $ArNO_2$ solutions in various concentrations. The dependence of the extinction on the $ArNO_2$ concentration (expressed in arbitrary units) is given in Fig. 1. The absolute concentration of $ArNO_2$ was about $2 \cdot 10^{-3}$

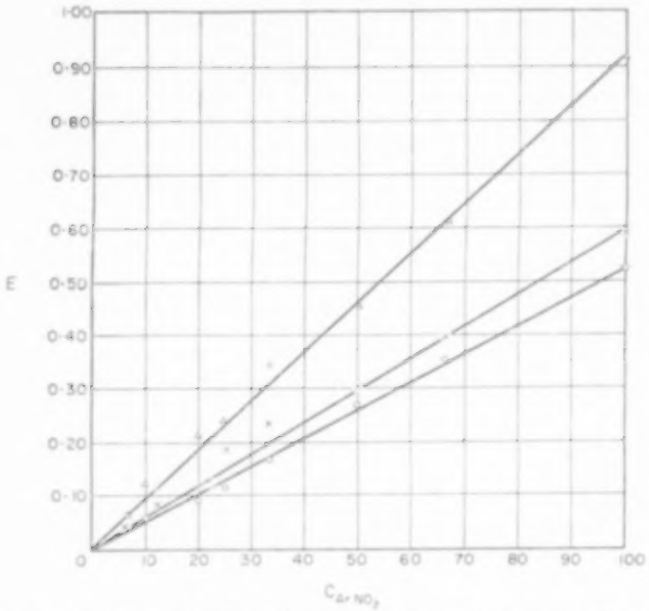


FIG. 1. Test of validity of the Beer's law. Dependence of the extinction E on the $ArNO_2$ concentration in solutions: △ HNO_3 7·0 M + H_2O, ○ HNO_3 3·1 M + H_2SO_4 4·9 M + H_2O, × HNO_3 5·8 M + $HClO_4$ 5·0 M + H_2O.

mole/l. The results show the extinction coefficient as constant during the investigation. The differences in the slope could arise from the initial concentration difference and from the dependence of ε on the medium, but does not preclude the application of Lambert-Beer's law to every mixture under investigation.

Measurement of the reaction rate

The nitrating mixture was introduced into one cell of photo-colorimeter. ArH was added to a portion of the same nitrating mixture, the solution introduced into the second cell of the colorimeter and the extinction readings taken at regular time intervals and when the extinction value became constant all the dissolved ArH was assumed nitrated. On the basis of Lambert-Beer's law it was possible to determine the fraction of ArH nitrated in times t_1, t_2 etc. If ε and h are constant, then

$$\frac{E_t}{E_\infty} = \frac{c_t}{c_\infty}$$

where E_t and E_∞ are the extinctions at times t and t_∞, respectively; c_t/c_∞ is the fraction of ArH nitrated in the time t. In some cases t_∞ was of the order of several hours.

Determination of the reaction order

In all the solutions investigated the nitric acid greatly exceeded the ArH concentration and thus, the first order reaction was to be expected. It was checked by means of the fractional life method

$$t_{1/n} \sim \frac{1}{a^{s-1}}$$

where $t_{1/n}$ is the fractional life time ($n = 1, 2, 3, 4, \ldots$), a is the initial reactant concentration, s is the reaction order. The fractional life times are: (a) proportional to a for the

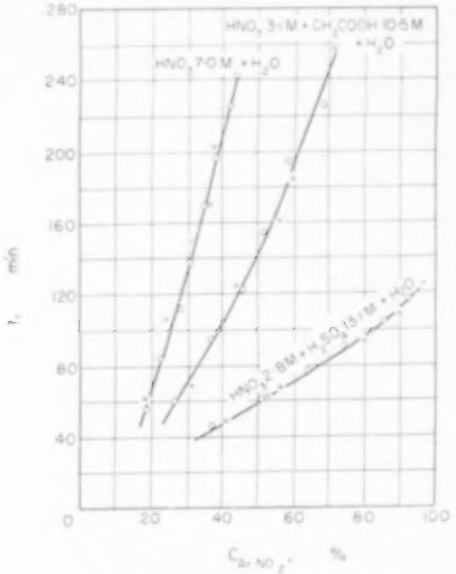


FIG. 2. Determination of the reaction order by means of the fractional life method.
×—initial ArH concentration = a, ○—initial ArH concentration = $2a$.

zero order reactions, (b) independent of a for the first order reactions, (c) inversely proportional to a for the second order reactions.

The dependence of $ArNO_2$ concentration on the nitration time was determined in two parallel series, one having the initial ArH concentration equal to a and the other to $2a$. The results given in Fig. 2 show the fractional life time to be independent of the initial concentration of ArH. Thus the reaction is of the first order.

Calculation of the reaction rate constant

In the equation for the first order reaction

$$\ln \frac{a}{a - c_t} = k_1 t$$

the nitration was assumed complete, thus the initial ArH concentration equalled the final $ArNO_2$ concentration, $a = c_\infty$. Then

$$2{\cdot}303 \log \frac{1}{1 - c_t/c_\infty} = k_1 t$$

Since $c_t/c_\infty = E_t/E_\infty$ the expression of the rate constant is

$$k_1 = -\frac{2{\cdot}303}{t} \log (1 - E_t/E_\infty)$$

In the course of each nitration it was possible to make about 10 measurements and each nitrating solution was examined twice. Thus the values k_1 given in Table 1 are the average of 14–20 measurements. The average error was estimated to be ±7 per cent.

TABLE 1. NITRATION RATE CONSTANTS IN THE INVESTIGATED SOLUTIONS
($c_{ArH} = 1{\cdot}4 \times 10^{-3}$ mole/l.)

No.	Concentration, mole/l.					$\xi = \frac{\Sigma[HX]}{[H_2O]}$	Rate constant $10^5 k_1$ sec^{-1}	Medium
	HNO_3	CH_3COOH	H_2SO_4	$HClO_4$	H_2O			
1	4·0	—	—	—	48·7	0·08	1·9	
2	6·3	—	—	—	44·8	0·14	3·9	$HNO_3 + H_2O$
3	10·0	—	—	—	37·7	0·26	4·5	
4	3·1	10·5	—	—	17·7	0·77	7·7	$HNO_3 +$
5	2·9	13·6	—	—	8·2	2·01	11·7	$CH_3COOH +$
6	5·4	12·5	—	—	5·5	3·26	13·0	H_2O
7	3·0	15·3	—	—	—		16·9	
8	3·1	—	4·9	—	38·0	0·21	3·7	
9	3·2	—	7·7	—	30·0	0·36	4·4	$HNO_3 +$
10	3·0	—	9·7	—	25·0	0·51	4·7	$H_2SO_4 +$
11	2·8	—	13·1	—	15·2	1·05	20·3	H_2O
12	2·8	—	14·9	—	7·9	2·24	46·1	
13	6·2	—	4·8	—	31·8	0·35	5·0	
14	6·1	—	10·0	—	14·8	1·09	10·8	
15	3·2	—	—	2·8	43·0	0·14	5·1	
16	2·8	—	—	7·2	32·3	0·31	6·2	$HNO_3 +$
17	6·0	—	—	3·4	29·2	0·32	5·1	$HClO_4 +$
18	5·8	—	—	5·0	30·2	0·36	5·9	H_2O
19	0·9	—	—	8·7	32·2	0·30	2·9	
20	2·7	—	14·6	P_2O_5 0·8	5·4	3·50	102·6	$HNO_3 + H_2SO_4 + P_2O_5 + H_2O$

DISCUSSION

According to Ingold *et al.*[5] in the nitrating mixture which does not allow the formation of NO_2^+ ions because of too great water concentration, the nitrating agent is the $H_2NO_3^+$ ion. Ingold based his conclusion on a sudden great change of the nitration rate constant k_1 caused by only a small concentration change of the nitration mixture components. He maintains that nitric acid is a base in relation to H_2SO_4 or $HClO_4$, water is a base in relation to HNO_3, H_2SO_4 and $HClO_4$. Water causes hydration and dissociation of the acids beginning with the strongest one. When the concentration of the strong acid exceeds that of free water, the acid excess reacts with nitric acid to form the $H_2NO_3^+$ ions, the nitrating agent.

Preliminary analysis of the results in Table 1 are apparently in agreement with Ingold's. A function ξ can be formed, defined as the ratio of the sum of all acid concentrations [HX] (including HNO_3) to the water concentration, $\xi = \Sigma[HX]/[H_2O]$. Nitric acid is included because it is both an acid and a base.[6]

Fig. 3 shows the dependence of k_1 on ξ. A sudden increase of k_1 takes place at the value $0{\cdot}70 < \xi < 1{\cdot}00$.

According to Ingold[5] one can calculate that the 2-phenylethylsulphonic acid nitrated showed the sudden increase of k_1 at the value $0{\cdot}36 < \xi < 0{\cdot}44$. In the

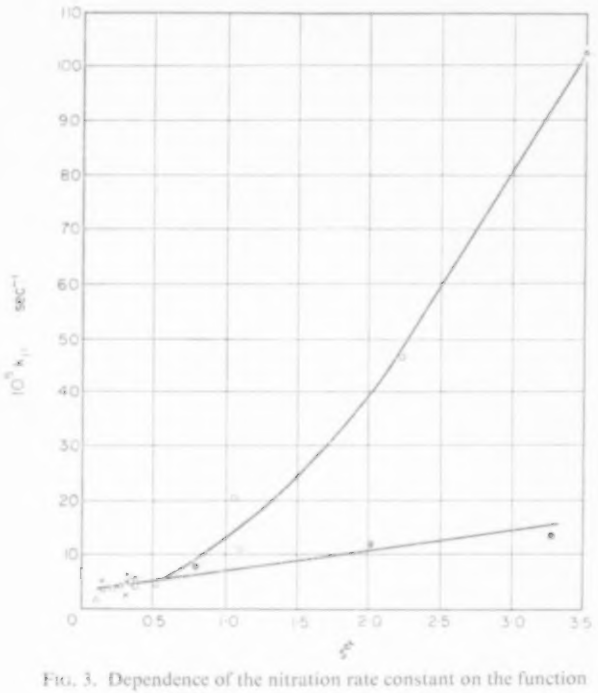


FIG. 3. Dependence of the nitration rate constant on the function

$$\xi = \frac{\Sigma[HX]}{[H_2O]}$$

△ $HNO_3 + H_2O$, ● $HNO_3 + CH_3COOH + H_2O$,
○ $HNO_3 + H_2SO_4 + H_2O$, × $HNO_3 + HClO_4 + H_2O$,
* $HNO_3 + H_2SO_4 + P_2O_5 + H_2O$.

nitration of N-acetyl-2-naphthylamine, if the $H_2NO_3^+$ ion were the nitrating agent formed according to Ingold at the value $\xi = 0{\cdot}4$, a k_1 change would occur in the same range of ξ.

Secondly, during nitration with $HNO_3 + CH_3COOH + H_2O$ mixture, the $H_2NO_3^+$ ion cannot be formed as acetic acid is a base in relation to HNO_3. Nevertheless, an increase of k_1 was observed although not so sudden as in the case of H_2SO_4, but nevertheless pronounced.

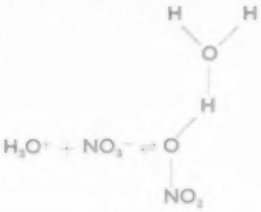
A better explanation of the experimental facts and not contrary to Ingold's hypotheses is that an increase of acid concentration and at the same time a decrease

[6] C. K. Ingold and D. J. Millen, *J. Chem. Soc.* 2612 (1950).

of water concentration in the nitrating medium results in the following reactions:
First by the dehydration of H_3O^+ ions

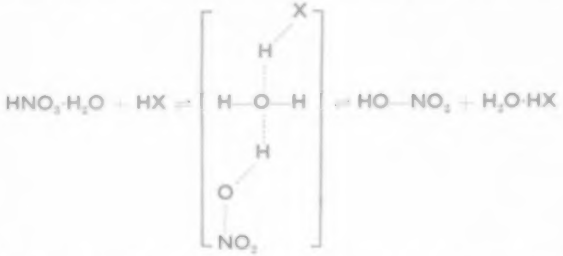
$$(H_3O^+)\cdot(nH_2O) + nHX \rightleftharpoons (n+1)\,H_3O^+ + nX^- \quad (1)$$

followed by depressed dissociation of HNO_3



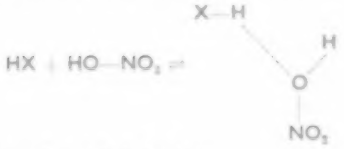
(2)

A further increase of acid concentration causes the dehydration of HNO_3



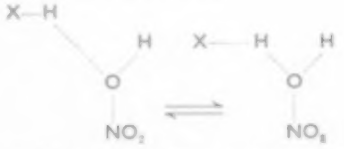
(3)

The final stage is the dehydration of the acid HX and its interaction with $HO—NO_2$ as a base



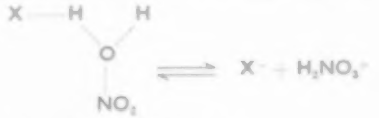
(4)

when the HX is a strong enough acid, it follows



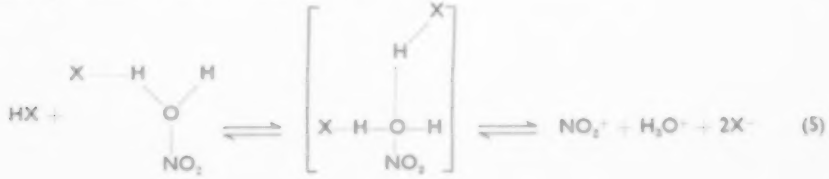
(4a)

and if there was a possibility of solvation, dissociation results



(4b)

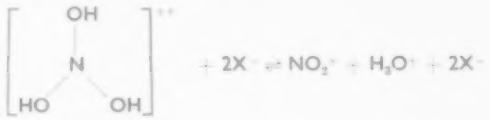
the last stage leads to the nitronium ion formation



(5)

This scheme is based on Brønsted's protolytic reactions. It is considered[7] that the initial stage of a protolytic reaction is the formation of a hydrogen bond between an acid and a base. A complete proton transfer and the following dissociation into ions depends on the presence of a solvating agent and does not always take place. In the protolytic scheme hydrogen bonding is essential and the introduction of a proton into the nitric acid molecule causes a gradual polarization and weakening of the HO—NO_2 bond that leads finally to a break down of the bond and to the formation of NO_2^+ ion solvated by X^- ions. A similar conclusion was drawn in previous work[3,4] from the changes in Raman spectrum of the solutions and it should be stressed that the changes depended on the acidity of the medium.

An objection to this hypothesis is the assumption that two oxygen atoms in the nitric acid molecule do not take part in the hydrogen bond formation, but if they did, the NO_2^+ ion formation according to the equation



would not be possible, yet the existence of NO_2^+ ion has been proved.[8]

Further support for the proposed mechanism may be found in the bond length difference between the oxygen and nitrogen atoms in the HNO_3 molecule: the N—OH bond, $r = 1{\cdot}405$ Å, is much longer than both N—O bonds, $r = 1{\cdot}206$ Å,[9,10] so the oxygen atom of OH is bound more weakly to the nitrogen and the hydrogen bond formation is therefore easier.

The sudden change in the nitration rate constant

The activation energy of nitration is the smaller, the weaker the HO—NO_2 bond. It also depends on the ease with which the proton detaches from the nitrated ArH. The possibility of hydrogen bond formation between the acid and ArH by the substituents or even π-electrons[7,11] must be taken into account. Hetherington and Masson[12] mentioned the role of interaction between ArH and the acid in nitration. It seems obvious that the sudden change of k_1 sets in when the thermal motion energy approaches the activation energy arising from the given nitration conditions. It is also obvious that the k_1 change will occur in an acidity range characteristic of any given ArH. Furthermore, if the acidity is too great, the proton detachment from ArH can be more difficult in some cases. Thus, the optimum concentration range of the nitrating mixture is adequate in one of the (2) to (5) stages in the protolytic scheme, depending on the properties of the nitrated ArH.

The $H_2NO_3^+$ ion could be the nitrating agent but its presence in the nitrating solution is not necessary and its existence has not yet been optically proved. Ingold stated that the $H_2NO_3^+$ ion spectrum could not be identified, like the H_3O^+ ion, the

[7] A. I. Šatenštejn, *Usp. Khim.* **24**, 377 (1955).
[8] C. K. Ingold *et al.*, *J. Chem. Soc.* 2504 (1950); *Ibid.* 2552 (1950); *Ibid.* 2576 (1950).
[9] L. R. Maxwell and V. M. Mosley, *J. Chem. Phys.* **8**, 738 (1940).
[10] D. J. Millen and J. R. Morton, *J. Chem. Soc.* 1523 (1960).
[11] W. G. Schneider, *Hydrogen Bonding*. Papers of Symposium at Ljubljana 1957, p. 55. Pergamon Press (1959).
[12] J. A. Hetherington and I. Masson, *J. Chem. Soc.* 105 (1933).

frequency of proton exchange was so high that formation of definite vibration levels was prevented. This argument cannot be accepted as then no spectrum would be observed in the $HNO_3 \cdot H_2O$ system, since by the proton exchange the H_2O molecule would pass into the H_3O^+ ion just as frequently as the HNO_3 into the NO_3^-. Nevertheless, the spectrum of $HNO_3 \cdot H_2O$ was observed and in the liquid state it consisted of the spectra of HNO_3 and H_2O molecules, whereas in the solid state there were observed in the spectrum the NO_3^- and H_3O^+ bands[13,14] and thus the identification of the H_3O^+ ion spectrum was achieved.[14,15]

It is well known[16] that compounds such as BF_3, $AlCl_3$ accelerate nitration. They cannot cause the formation of $H_2NO_3^+$ ions, but instead may weaken the $HO—NO_2$ bond by attracting the OH-oxygen electrons and can cause the NO_2^+ formation in accordance with the protolytic scheme.

Urbański and Hackel[17] investigated the O-nitration kinetics of starch and observed that nitration takes place in the absence as well as in the presence of NO_2^+ ions. The nitration rate increases continuously when passing from the solutions without NO_2^+ ions to the solutions in which the NO_2^+ ions can be formed. Except for the NO_2^+ ion they assume the nitrating agent could be the $HO—NO_2$ molecule in accordance with the protolytic scheme.

Finally, the effect of dehydrating agents on the nitration kinetics will be discussed. Martinsen[18] pointed out that an addition of P_2O_5 to the $HNO_3 + H_2SO_4 + H_2O$ mixture did not change the nitration rate constant to any extent. In the protolytic scheme P_2O_5 would favour the dehydration of H_3O^+ stage (1) and of HNO_3 molecules stage (3). Furthermore, P_2O_5 would form phosphoric acid thus increasing the acidity of the medium.

The k_1 was measured in a $HNO_3 + H_2SO_4 + H_2O$ solution after addition of P_2O_5 (No. 20 in Table 1) and a considerable increase of k_1 corresponding to the increase of ξ value (Fig. 3) was observed.

The ξ function might have been an important property for the nitration process as a value defining the medium acidity if it contained not only the concentrations but also the strength of acids and bases. In its present form it has a limited significance only.

EXPERIMENTAL

The reagents used were: nitric acid, $d = 1{\cdot}39$; sulphuric acid, $d = 1{\cdot}84$; perchloric acid, $d = 1{\cdot}54$; glacial acetic acid; acetic acid anhydride; phosphorous pentoxide; all commercial grades and used without further purification.

The acid sum concentration in the solutions was determined by acidimetric analysis; the concentration of nitric acid—by nitrometric method; the concentration of water—by density measurements.

Acetic acid anhydride was used to prepare a nonaqueous solution of $HNO_3 + CH_3COOH$ (No. 7 in Table 1).

N-acetyl-2-naphthylamine, m.p. 133°, dissolved in a mixture of acetic acid with water (1:1) was a basic solution of ArH, with concentration of $2{\cdot}8 \times 10^{-4}$ mole/l. This solution was added to the nitrating mixtures in a ratio of 1:20. Thus the concentration of ArH in the nitrating mixtures was $1{\cdot}4 \times 10^{-5}$ mole/l.

The extinction measurements were carried out by a Pulfrich photocolorimeter with a vertical

[13] A. Simon and M. Weist, *Z. Anorg. Chem.* **268,** 301 (1952).
[14] D. E. Bethell and N. Sheppard, *J. Chem. Phys.* **21,** 1421 (1953).
[15] R. C. Taylor and G. L. Vidale, *J. Amer. Chem. Soc.* **78,** 5999 (1956).
[16] A. V. Topčiev, *Nitrovanie uglevodorodov i drugich organičeskich soedinenij*. Moskva (1956).
[17] T. Urbański and J. Hackel, *Tetrahedron* **2,** 300 (1958).
[18] H. Martinsen, *Z. Phys. Chem.* **59,** 605 (1907).

light path. Cylindrical glass cells were used. The length of the absorbing path was 10 mm constant. A blue filter (470 mμ) was applied for all the measurements. An iron ring sealed in glass was placed in the cell and moved vertically with an electromagnet to mix the nitrating solution. It did not disturb the light path. The temperature was kept constant at 20 ± 2°.

Acknowledgements—The author is indebted to Professor Dr. S. Minc for encouragement and valuable advice. He also wishes to thank Dr. A. Szuchnik, Department of Organic Chemistry, University of Warsaw, for the help in the choice and for supplying N-acetyl-2-naphthylamine, and Z. Kuźma, this Department, for carrying out the measurements.

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THE ELECTRONIC SPECTRA OF THE NITRONAPHTHYLAMINES

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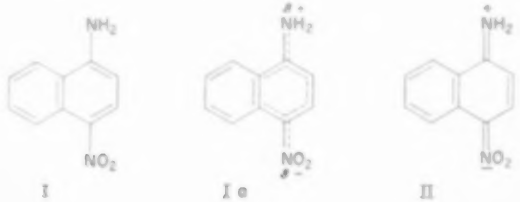
Abstract—The ultra-violet absorption spectra of all fourteen nitronaphthylamines have been measured in polar and non-polar solvents. The first absorption band undergoes a bathochromic shift on changing from a non-polar to a polar solvent. An attempt has been made to correlate the magnitude of this bathochromic shift with mesomeric interaction and intramolecular hydrogen bonding in the nitronaphthylamines.

INTRODUCTION

THE ultra-violet absorption spectra of pure specimens of the nitronaphthylamines have been measured, using a photoelectric spectrophotometer, in cyclohexane and ethanol solutions. This is the first occasion that the spectra of all fourteen nitronaphthylamine isomers have been reported and previous studies[1–3] of these compounds have used the photographic recording method.

The first absorption band of the nitronaphthylamines, which is due to mesomeric interaction between the nitro and amino groups, undergoes a large bathochromic shift on changing from a non-polar to a polar solvent. In the ground state, in a non-polar solvent, a nitronaphthylamine molecule can be represented by state I. On changing to a hydrogen bonding, polar solvent, such as ethanol, the same nitronaphthylamine molecule may be represented by state Ia, due to the development of partial charges by mesomeric interaction. When light is absorbed the molecule is raised to the first excited state II; this change is observed as the first absorption band.



I Ia II

The energy difference between states Ia and II is less than that between states I and II. Hence less energy is required to excite a nitronaphthylamine molecule in a polar than in a non-polar solvent thus explaining the observed bathochromic shift. In nitronaphthylamine molecules where intramolecular hydrogen bonding occurs, between an oxygen atom of the nitro group and a hydrogen atom of the amino group, solvation is reduced leading to a smaller bathochromic shift.

Mesomeric interaction in the nitronaphthylamines results from the conjugation of

[1] L. Hertel-Danzig, *Z. Electrochem.* **47**, 813 (1941).
[2] H. H. Hodgson and H. S. Turner, *J. Soc. Dyers and Colourists* **59**, 218 (1943).
[3] H. H. Hodgson and D. E. Hathway, *Trans. Faraday Soc.* **41**, 115 (1945).

the lone pair of electrons on the amine nitrogen atom, through the π-electron system of the naphthalene nucleus with the p-electron system of the nitro group. The energy difference between a hypothetical nitronaphthylamine in which mesomeric interaction does not occur, possibly almost true for the 7- and 3-nitro-2-naphthylamines, and a nitronaphthylamine in which it does occur can be termed the energy of mesomeric interaction. The energy of mesomeric interaction would thus be determined by the distribution of π-electrons in the naphthalene nucleus and the conjugating powers of the carbon atoms to which the nitro and amino groups are attached.

Remington[4] and also Wepster[5] have used the intensity of the first absorption band of substituted nitranilines as a measure of mesomeric interaction and hence steric distortion of the substituent groups. Wepster[5] has used the criterion that the energy of mesomeric interaction in a *p*-nitraniline molecule, substituted by alkyl groups *ortho* to the nitro group, is proportional to the square of the cosine of the angle by which the nitro group is twisted away from the plane of the aromatic nucleus. The extinction coefficient of the first absorption band of these substituted *p*-nitranilines was found to be proportional to the energy of mesomeric interaction.

In the nitronaphthylamines fourteen different modes of mesomeric interaction through the naphthalene nucleus are possible. From the results discussed later it seems probable that the energies of mesomeric interaction in the nitronaphthylamines may also be related to the extinction coefficients of their first absorption bands.

Before discussing the interpretation of the absorption spectra of the nitronaphthylamines the spectra of some monosubstituted naphthalene compounds and the analogous nitranilines are mentioned.

The Spectra of the Nitronaphthylamines

(1) *Monosubstituted naphthalene compounds*

Details of the absorption spectra of some monosubstituted derivatives of naphthalene have been collected in Table 1. The nomenclature used to designate the absorption bands is that of Clar[6] (cf Peters[7]). When a substituent is in the 1-position the p-band undergoes a larger bathochromic shift, relative to the p-band of naphthalene, than when the same substituent is in the 2-position. Also the p-band of a 1-substituted compound is usually more intense than that of the corresponding 2-isomer. When however a "powerful" electronic substituent, eg. $-NH_2$, $-NO_2$, or $-CO_2H$, is in the 1-position then the p- and α-bands merge into a single band (pα). The merged pα-band may then be less intense than the p-band of the 2-isomer but oscillator strength is probably a better criterion in such cases.

These differences between the spectra of 1- and 2-isomers of monosubstituted naphthalene compounds may be related to the greater conjugating power of the 1-position. Coulson and Longuet-Higgins[8] have defined the conjugating power of a position, in an aromatic nucleus, as β times the self polarizability of that position (β is here the resonance integral). In naphthalene the self polarizability of the 1-position is 0·443 whilst that of the 2-position is 0·405 (compared with 0·398 in benzene).

[4] W. R. Remington, *J. Amer. Chem. Soc.* **67**, 1838 (1945).
[5] B. M. Wepster, *Steric Effects in Conjugated Systems* p. 82. Butterworths, London (1959).
[6] E. Clar, *Aromatische Kohlenwasserstoffe*. Springer-Verlag, Berlin (1941).
[7] D. Peters, *J. Chem. Soc.* 646, 1993 and 4182 (1957).
[8] C. A. Coulson and H. C. Longuet-Higgins, *Proc. Roy. Soc.* A **195**, 188 (1948).

TABLE 1. MAXIMA IN THE SPECTRA OF MONOSUBSTITUTED NAPHTHALENE

Substituent	Compounds: Absorption maxima (mμ) β-band	p-band	α-band	Solvent	Ref.
H	220 (5·0)	276 (3·75)	311 (2·90)	ethanol	9
1-CH_3	221 (4·85)	282 (3·80)	314 (2·58)		
2-CH_3	221 (4·95)	276 (3·68)	319 (2·68)	ethanol	10
1-OH	233 (4·52)	295 (3·71)	323 (3·43)		
2-OH	226 (4·86)	276 (3·67)	325 (3·27)	ethanol	11
1-F		277 (3·81)	317		
2-F		270 (3·79)	321	n-hexane	12
1-Cl		281 (3·90)	314		
2-Cl		277 (3·79)	317	n-hexane	12
1-I	227 (4·60)	287 (4·03)	316		
2-I	230 (4·40)	276 (3·88)	323	n-heptane	12,13
1-NH_3^+		278 (3·85)	313 (2·60)		
2-NH_3^+	221 (5·01)	276 (3·75)	311 (2·60)	ethanolic HCl	14,9
1-NH_2	240 (4·37)	321* (3·20)			
2-NH_2	237 (4·80)	283 (3·80)	339 (3·30)	ethanol	15
1-NO_2	243 (3·94)	331* (3·63)			
2-NO_2	261 (4·36)	303 (3·92)	349 (3·42)	ethanol	16
1-CO_2H		294* (3·87)			
2-CO H	234 (4·70)	280 (3·80)	333 (3·10)	ethanol	15
1-SO_3H	224 (4·84)	279 (3·80)	315 (2·63)		
2-SO_3H	227 (5·0)	274 (3·69)	316 (2·55)	ethanolic HCl	11

Log *E* values are in parentheses. * indicates the centre of a merged pα-band.

[9] R. N. Jones, *J. Amer. Chem. Soc.* **67**, 2127 (1945).
[10] R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds* Figs. 196, 197. John Wiley, New York (1951).
[11] C. Daglish, *J. Amer. Chem. Soc.* **72**, 4859 (1950).
[12] J. Ferguson, *J. Chem. Soc.* 304 (1954).
[13] T. M. Dunn and T. Iredale, *J. Chem. Soc.* 1595 (1952).
[14] P. Ramert-Lucas, *Bull. Soc. Chim.* **17**, 262 (1950).
[15] Y. Hirshberg and R. N. Jones, *Canad. J. Res.* B **27**, 437 (1949).
[16] E. R. Ward and A. Hardy. Personal communication.

(2) *Spectra of the nitranilines*

Maxima occurring in the absorption spectra of the three nitranilines have been collected in Table 2. The values for ethanol solutions were collected from the literature and the spectra were measured in cyclohexane.

As neither aniline or nitrobenzene show any absorption above Log $E = 2{\cdot}0$, in the region 325–375 mμ, then the intense long wavelength absorption of the three nitranilines can be attributed to mesomeric interaction between the substituents. Using the

TABLE 2. MAXIMA IN THE SPECTRA OF THE NITRANILINES

Isomer	Absorption maxima (mμ)	
	Ethanol[5,18]	Cyclohexane
o-nitraniline	231 (4·22) 276 (3·69) 403 (3·72)	229 (4·26) 270 (3·69) 377 (3·70)
m-nitraniline	234 (4·20) 374 (3·18)	228 (3·86) 346 (3·26)
p-nitraniline	229 (3·79) 376 (4·19)	228 (4·18) 325 (4·10)

criterion previously mentioned, i.e. the intensity of the first absorption band, as a guide to mesomeric interaction the order for the three nitranilines is:

$$p > o > m.$$

This is the expected order of interaction in these compounds.[17] The first absorption band of *p*-nitraniline under goes a bathochromic shift of 51 mμ on changing from cyclohexane to ethanol.

o-Nitraniline has three absorption bands in the region measured whilst the *meta* and *para* isomers have only two. The additional absorption band in the spectrum of *o*-nitraniline is at 270 mμ. It probably arises from steric hindrance, between the adjacent nitro and amino groups, resulting in the absorption bands of aniline, nitrobenzene and possibly the forbidden band of benzene, compounded together, appearing in the spectrum of *o*-nitraniline.

(3) *The nitronaphthylamines*

Details of the maxima in the absorption spectra of the nitronaphthylamines, measured in ethanol and cyclohexane, are shown in Table 3.

Differences in the conjugative powers of the 1- and 2-positions in the naphthalene molecule have already been mentioned. In addition steric hindrance can occur between adjacent groups in the 1- and 2-, the 2- and 3-, and the 1- and 8-positions. Steric hindrance is greater in the 1- and 8-"peri" positions than in adjacent positions on the same nucleus. In fact the large nitro group, when in the 1-position, is sterically hindered even by a hydrogen atom in the 8-position.[19]

[17] C. K. Ingold, *Structure and Mechanism in Organic Chemistry* p. 223ff. Bell, London (1953).
[18] W. A. Schroeder, P. E. Wilcox, K. N. Trueblood and A. O. Dekker, *Analyt. Chem.* **23**, 1746 (1951).
[19] A. Fischer, W. Mitchell, G. S. Ogilvie, J. Packer, J. E. Packer and J. Vaughan, *J. Chem. Soc.* 1426 (1958).

In the homonuclear nitro-1-naphthylamines, in both ethanol and cyclohexane solutions, the intensities of the first absorption bands fall in the order:

$$4 > 2 > 3,$$

(where the number indicates the position of the nitro group). This is the same sequence as was observed for the nitranilines. Where the substituent groups are in different nuclei the intensity of the first absorption band gives the order of mesomeric interaction as:

$$7 > 5 = 6 > 8.$$

In fact 7-nitro-1-naphthylamine has a more intense first absorption band than 3-nitro-1-naphthylamine. The very low absorption of 8-nitro-1-naphthylamine is not surprising because solid models (Catalin) suggest that both the nitro and amino group are twisted away from the plane of the aromatic nucleus by 80–90.°

Thus the overall series for mesomeric interaction in the nitro-1-naphthylamines, from the intensities of their first absorption bands, is:

$$4 > 2 > 7 > 3 > 5 = 6 > 8.$$

TABLE 3. MAXIMA (mμ) IN THE SPECTRA OF THE NITRONAPHTHYLAMINES

(a) *The* X-*nitro*-1-*naphthylamines*

X	Ethanol	Cyclohexane	Difference, $\Delta\lambda$
2	222 (4·38)	221 (4·41)	1
	278 (4·22)	272 (4·14)	6
	428 (3·95)	404 (3·87)	24
3	224 (4·47)	221 (4·48)	3
	275 (4·10)[a]	265 (4·10)	10
	416 (3·43)	382 (3·54)	34
4	260 (4·00)[a]	251 (4·21)	9
	430 (4·25)	377 (4·07)	53
5	272 (4·01)	265 (4·06)	7
	336 (3·34)	340 (3·32)	4
	416 (3·34)	385 (3·43)	31
6	222 (4·47)	220 (4·54)	2
	296 (4·25)	280 (4·33)	16
	412 (3·35)	385 (3·47)	27
7	224 (4·50)	222 (4·53)	2
	288 (4·28)	277 (4·37)	11
	436 (3·62)	401 (3·65)	35
8	232 (4·23)[b]	229 (4·28)	3
	266 (3·88)[b]	259 (4·13)[b]	7
	332 (3·46)	330 (3·48)	2
	400 (3·21)	384–396 (3·30)	ca. 10

(b) *The* Y*-nitro-2-naphthylamines*

Y	Ethanol	Cyclohexane	Difference, $\Delta\lambda$
1	231 (4·56)	232 (4·56)	1
	262 (4·22)	261 (4·16)	1
	318 (3·62)	322 (3·65)	4
	419 (3·84)	396 (3·72)	23
3	234 (4·56)	232 (4·56)	2
	268 (4·27)[a]	264 (4·29)[a]	4
	330 (3·79)	320 (3·74)	10
	460 (3·29)	437 (3·25)	23
4	226 (4·58)	225 (4·56)	1
	263 (4·01)[b]	254 (4·00)[b]	9
	406 (3·51)	383 (3·50)	23
5	233 (4·45)	229 (4·44)	4
	274 (4·28)	268 (4·32)	6
	344 (3·56)	334 (3·54)	10
	397 (3·31)[b]	372 (3·42)[b]	25
6	234 (4·56)	226 (4·51)	8
	258 (4·13)[b]	258 (4·23)[b]	0
	294 (3·80)	280 (4·07)	14
	405 (4·15)	365 (4·13)	40
7	230 (4·41)	226 (4·40)	4
	270 (4·34)	268 (4·34)	2
	296 (4·25)	284 (4·23)	12
	410 (3·04)	380 (3·13)	30
8	234 (4·32)	234 (4·65)	0
	272 (4·21)	258 (4·24) 266 (4·23)	ca. 10
	430 (3·69)	392 (3·70)	38

[a]denotes the approximate centre of a split peak.
[b]denotes a minor maximum.

The order of interaction moments, from dipole moment measurements of the nitro-1-naphthylamines in benzene,[20] is:

$$4 > 2 > 7 > 3 = 5 = 6 > 8.$$

The interaction moments of 3-, 5-, and 6-nitro-1-naphthylamine all lie within 0·02 D. of each other and as this value is within the experimental error of the method these isomers can be considered to have equal moments. These series for mesomeric interaction are in some measure of agreement with the classical structures that can be written for excited states of the nitronaphthylamines, eg. a *para* quinonoid structure for 4, an *ortho* quinonoid for 2, an *ortho–para* quinonoid for 7, and a doubly *ortho* quinonoid structure for 5-nitro-1-naphthylamine.

[20] S. Walker and J. H. Richards. Personal communication.

The nitro-2-naphthylamines form a less satisfactory series in that the spectra and dipole results do not agree so well. In the homonuclear nitro-2-naphthylamines the intensities of the first absorption bands are in the order:

$$1 > 4 > 3.$$

4-Nitro-2-naphthylamine is a *meta* compound and the low double bond order of the 2,3-bond in naphthalene is in agreement with the low mesomeric interaction indicated for 3-nitro-2-naphthylamine.

The nitro-2-naphthylamines in which the substituent groups are in different nuclei form the series:

$$6 > 8 > 5 > 7$$

for the intensities of their first absorption bands. Indeed 6-nitro-2-naphthylamine has a more intense first absorption band than 1-nitro-2-naphthylamine. The complete order of mesomeric interaction in the nitro-2-naphthylamines, as judged by the intensity of their first absorption bands is thus:

$$6 > 1 = 8 > 4 > 5 > 3 > 7.$$

The order of interaction moments, from dipole moment measurements of the nitro-2-naphthylamines in benzene,[20] is

$$7 > 1 = 8 > 6 > 5 > 4 > 3.$$

The main difference between these two series for the nitro-2-naphthylamines is the position of 7-nitro-2-naphthylamine. On the basis of classical structures a doubly *para* quinonoid structure can be written for 6, an *ortho* quinonoid for 1, and an *ortho–para* quinonoid structure for 8-nitro-2-naphthylamine. A quinonoid structure cannot be written for 7-nitro-2-naphthylamine and hence the large interaction moment for this compound is surprising.

In cyclohexane the first absorption band of *o*-nitraniline is at a considerably longer wavelength than the corresponding band for the other two isomers. A similar situation is found with 2-nitro-1-naphthylamine and 3-nitro-2-naphthylamine. It seems that when two groups which interact are adjacent on an aromatic nucleus then less energy is required to reach the first excited state. Such an effect is easily masked by solvation in a polar solvent.

By analogy with *o*-nitraniline sterically hindered 2-nitro-1-naphthylamine would be expected to show some evidence of a "break through" spectrum of 1-naphthylamine and/or 2-nitronaphthalene. In cyclohexane 2-nitro-1-naphthylamine has a broad absorption band with a maximum at 272 mμ and extending to 320 mμ (3-and 4-nitro-1-naphthylamines have narrower absorption bands at 265 and 251 mμ respectively). This broad band extending to 320 mμ may be evidence for a "break through" of the spectrum of 1-naphthylamine (maximum at 321 mμ) but not that of 2-nitronaphthalene (maximum at 349 mμ). A similar situation is found in the homonuclear nitro-2-naphthylamines. The 1- and 3-nitro-2-naphthylamines have absorption peaks at 318 and 330 mμ respectively whereas 4-nitro-2-naphthylamine shows no absorption in this region.

Solvent effects

The first absorption band, that due to mesomeric interaction, undergoes a bathochromic shift on changing from a non-polar to a polar solvent. In Figs. 1 and 2

this shift, $\Delta\lambda$, has been plotted against the intensity of the first absorption band, Log E, a probable measure of mesomeric interaction, for the nitro-1- and 2-naphthylamines respectively.

For the nitro-1-naphthylamines a reasonable straight line can be drawn through six of the seven points indicating that solvation is related to the development of partial charges, i.e. mesomeric interaction, in these molecules. The value of $\Delta\lambda$ for 2-nitro-1-naphthylamine is only 24 mμ whereas from its extinction coefficient it should be about

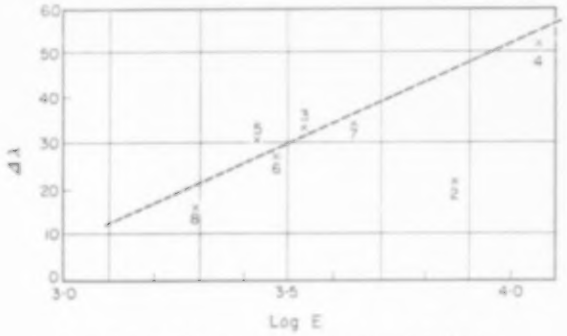


FIG. 1. Solvation of the nitro-1-naphthylamines.

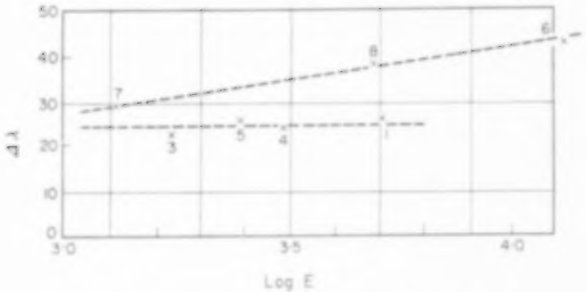


FIG. 2. Solvation of the nitro-2-naphthylamines.

45 mμ. This low value can be ascribed to the intramolecular hydrogen bonding of an oxygen atom of the nitro group with a hydrogen atom of the adjacent amine group.

Fig. 2 shows that the nitro-2-naphthylamines do not form such a well defined series as the nitro-1-naphthylamines. A possible means of correlating the results for the nitro-2-naphthylamines is indicated on the diagram. Thus solvation may be proportional to mesomeric interaction in the 6-, 7-, and 8-nitro-2-naphthylamines but the other isomers may be solvated to the same extent as the intramolecular hydrogen bonded isomer, 1-nitro-2-naphthylamine. An infra-red study by Hathway and Flett[21] suggests that intramolecular hydrogen bonding is present in both 2-nitro-1-naphthylamine and 1-nitro-2-naphthylamine; the former being more strongly hydrogen bonded than the latter. In the case of 1-nitro-2-naphthylamine the nitro group is sterically hindered by the 8-position hydrogen atom which may result in a weakening of the hydrogen bonding in this compound.

[21] D. E. Hathway and M. St. C. Flett, *Trans. Faraday Soc.* **45**, 818 (1949).

It would seem that as mesomeric interaction increases, the partial charges on the substituent groups increase, thus binding the solvent molecules more strongly into the system. Such partial charges are able to develop better in the 1-position of naphthalene due to the greater polarizability of the molecule from this position. Some recent nuclear magnetic resonance studies give a similar picture of solvation for substituted fluorobenzenes.[22]

EXPERIMENTAL

The ultra-violet absorption spectra were measured on a Unicam SP 500 photoelectric spectrophotometer. Commercial absolute ethanol was purified by filtration through silica gel and subsequent distillation. Cyclohexane was B.D.H. Spectroscopic Grade. The nitranilines were purified by recrystallization. Pure samples of the fourteen nitronaphthylamines were supplied by Dr. E. R. Ward.

Acknowledgements—The author wishes to thank Dr. E. R. Ward for his encouragement and Dr. S. Walker for helpful discussions and for providing the results of dipole moment measurements prior to their publication.

[22] R. W. Taft, R. E. Glick, I. Fox, S. Ehrenson and I. C. Lewis *J. Amer. Chem. Soc.* **82**, 756 (1960).

Tetrahedron, 1961, Vol. 12, pp. 41 to 50. Pergamon Press Ltd. Printed in Northern Ireland

THE TAUTOMERISM OF HETEROAROMATIC COMPOUNDS WITH FIVE-MEMBERED RINGS—I

5-HYDROXYISOXAZOLES–ISOXAZOL-5-ONES

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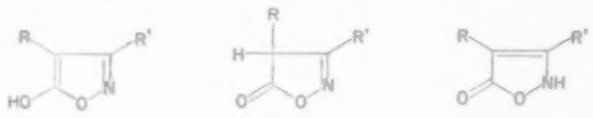
(*Received* 23 *August* 1960)

Abstract—Infra-red and ultra-violet spectra show that 3,4-dimethyl-5-hydroxyisoxazole exists in aqueous and chloroform solution, and in the solid phase in the OH form; and that 3-phenyl-, 4-bromo-3-phenyl-, and 4-methyl-3-phenyl-isoxazol-5-ones exist as mixtures of the CH and NH forms in solution, the proportion of the NH form increasing with the polarity of the solvent. The basicities of isoxazole and some of its derivatives are recorded. Isoxazol-5-ones are acids of comparable strength with carboxylic acids.

THE well-known reaction of β-ketoesters with hydroxylamine affords products which can be formulated as 5-hydroxyisoxazoles (I) or as 4H- (II) or 2H-isoxazol-5-ones (III)



I II III

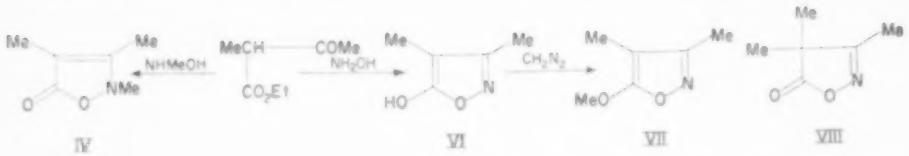
Early workers assigned structures on criteria now known to be unreliable, thus Uhlenhuth[1] favoured the NH structure (III) because the silver salt of 3-phenylisoxazol-5-one gave with methyl iodide a product (also obtained by methanol–sulphuric acid treatment of the isoxazolone) which he formulated as the N-methyl derivative (incorrectly, see below). Moureu and Lazennec[2] also preferred the NH structure on grounds of formation. Kohler and Blatt[3] found that 3,4-diphenylisoxazol-5-one when freshly dissolved in ethanol reacted with ca. 50 per cent of one molecule of bromine, but after standing with ca. 90 per cent and concluded that the solid was in the CH form (now disproved, see later) but that the OH form predominated in solutions; the NH form was held to be excluded by the results of ozonolysis. Confidence in the bromine titration method is undermined by the fact that 3-phenylisoxazol-5-one reacts rapidly with 1·9 moles of bromine.[4]

Physical methods were first used by Angyal and Le Fèvre[4]; the dipole moment of 3-phenylisoxazol-5-one (4·9 D) was nearer to that of the 4,4-dimethyl analogue (5·0 D) than to that of the 5-methyl compound (3·8 D) and although this was not regarded as conclusive evidence for the CH form, the infra-red spectra of the solids did show that the CH form (II) prevailed in the crystal. Infra-red spectral examination of the benzene solution in the 3800–2800 cm^{-1} region was stated to exclude the NH and the OH forms but this must be considered less conclusive because of poor solubility.

[1] R. Uhlenhuth, *Liebigs Ann.* **296**, 33 (1897).
[2] C. Moureu and I. Lazennec, *Bull. Soc. Chim. Fr.* (4) **1**, 1092 (1907).
[3] E. P. Kohler and A. H. Blatt, *J. Amer. Chem. Soc.* **50**, 504 (1928).
[4] C. L. Angyal and R. J. W. Le Fèvre, *J. Chem. Soc.* 2181 (1953).

Following work in this laboratory on potentially tautomeric pyridines and pyridine 1-oxides,[5] we have now studied the ultra-violet and infra-red spectra and basicities of a series of 5-hydroxyisoxazoles, or isoxazol-5-ones, and methylated derivatives of their three alternative tautomeric forms.

Preparation of compounds. Ethyl methylacetoacetate (V) and hydroxylamine afforded 3,4-dimethyl-5-hydroxyisoxazole (VI),[1] which gave a single methyl derivative



with diazomethane, shown to be 3,4-dimethyl-5-methoxyisoxazole (VII) by (a) the infra-red spectrum,[6] (b) methoxyl group shown by Zeisel analysis, and (c) non-identity with the N- and C-methyl derivatives. The silver and sodium salts of the isoxazolone also gave 3,4-dimethyl-5-methoxyisoxazole with methyl iodide. Diazoethane afforded the corresponding 5-ethoxy-derivative; this structure was confirmed by the infra-red spectrum. The acetoacetate (V) with N-methylhydroxylamine[7] gave unambiguously 2,3,4-trimethylisoxazol-5-one (IV); this use of N-methylhydroxylamine in isoxazolone synthesis is new although 2,4-diphenylisoxazol-5-one has been made analogously from phenylhydroxylamine.[8] Ethyl dimethylacetoacetate and hydroxylamine gave 3,4,4-trimethylisoxazol-5-one (VIII).[9]

The appropriate β-ketoesters and hydroxylamine gave 3-phenyl-,[10] 4-methyl-3-phenyl-,[11] and 4,4-dimethyl-3-phenyl-isoxazol-5-one.[11] 3-Phenylisoxazol-5-one with diazomethane,[12] or with methanol and sulphuric acid,[1] yielded 5-methoxy-3-phenyl-isoxazole,[13] but the sodium salt with methyliodide provided mainly the N-methyl derivative. 4-Methyl-3-phenylisoxazol-5-one with sodium ethoxide and methyl iodide gave the N-methyl derivative, the structure of which was proved by the infra-red spectrum, and a negative Zeisel analysis. Diazomethane afforded a mixture of ca. 35 per cent N-methyl and 65 per cent O-methyl derivative, as shown by infra-red spectroscopy; the methoxy- compound was isolated.

4-Bromo-3-phenylisoxazol-5-one[14] with diazomethane provided the N-methyl derivative. Bromine and 4-methyl-3-phenylisoxazol-5-one gave 4-bromo-4-methyl-3-phenylisoxazol-5-one; bromination of 3-phenylisoxazol-5-one gave the 4,4-dibromo-derivative[15] (*vide infra*).

Ultra-violet spectra (Table 1). The spectrum of 3,4-dimethyl-5-hydroxyisoxazole (Table 1, No. 4) as a neutral species resembles that of the 5-methoxy-analogue (No. 1) but differs from those of 2,3,4-, and 3,4,4-trimethylisoxazol-5-one (Nos. 3, 2). This

[5] J. N. Gardner and A. R. Katritzky, *J. Chem. Soc.* 4375 (1957); R. A. Jones and A. R. Katritzky, *J. Chem. Soc.* 3610 (1958); 1317 (1959); In press (1960).
[6] A. R. Katritzky and A. J. Boulton, *Spectrochim. Acta* In press.
[7] *Beilstein Hauptwerk* **4**, 534.
[8] H. Rupe and J. Grünholz, *Helv. Chim. Acta* **6**, 102 (1923).
[9] P. Billon, *Ann. Chim.* (10) **7**, 357 (1927).
[10] A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **24**, 502 (1891).
[11] A. Haller and E. Bauer, *C.R. Acad. Sci. Paris* **152**, 1446 (1911).
[12] E. Olivieri-Mandalà and A. Coppola, *Rend. Accad. Lincei* (5) **20** I, 248 (1911).
[13] P. Grünanger and M. R. Langella, *Gazz. Chim. Ital.* **89**, 1784 (1959).
[14] T. Posner, *Ber. Dtsch. Chem. Ges.* **39**, 3521 (1906).
[15] A. Meyer, *Ann. Chim.* (9) **1**, 315 (1914).

TABLE 1. ULTRA-VIOLET SPECTRA OF ISOXAZOLES AND ISOXAZOL-5-ONES

No.	Substituents at positions				Cyclohexane		Water		20 N H_2SO_4	
	2	3	4	5	$\lambda(m\mu)$	$\varepsilon \times 10^{-3}$	$\lambda(m\mu)$	$\varepsilon \times 10^{-3}$	$\lambda(m\mu)$	$\varepsilon \times 10^{-3}$
1	—	Me	Me	OMe	209	5·63	215	6·2	227	9·27
2	—	Me	Me_2.	:O	— [a]		201	4·2	201	4·16[d]
3	Me	Me	Me	:O	262	7·89	268	12·0	252	9·76
4	—	Me	Me	OH	213	6·58	224	6·25[b]	236	8·64
5	—	Ph	H	OMe	236	15·4	239	16·0	— [e]	
6	—	Ph	Me	OMe	228	12·6	231	10·7	275	16·1
7	—	Ph	Me_2	:O	254	10·1	253	13·5	256	10·3
8	Me	Ph	Me	:O	280 231	6·95 10·6	281 243	10·4 8·65	271	11·6
9	—	Ph	H_2	:O	253	14·1	254	13·6[b]	266	16·5
10	H	Ph	Me	:O	253	13·2	281 243	11·3[c] 9·4	274	14·9
11	H	Ph	Br	:O	274 224	6·95 7·66	287 238	7·65[e] 7·71	—	
12	—	Ph	Br, Me	:O	273 223	7·42 7·71	281 219	6·69 6·09	—	
13	—	Ph	Br_2	:O	290 226	6·47 8·30	— [f]		—	
14	Me	Ph	Br	:O	291 238	7·8 8·95	291 246	10·2 8·02	—	

[a] Band below solvent cut-off.
[b] Phosphate buffer pH 2 used, considerable proportion of anion present in water.
[c] Phosphate buffer pH 1·5.
[d] 10 N H_2SO_4 used to get sufficient transmission.
[e] Decomposed rapidly in acid.
[f] Decomposed.

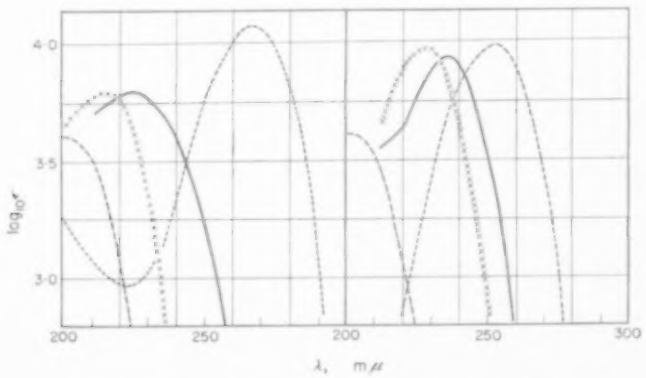


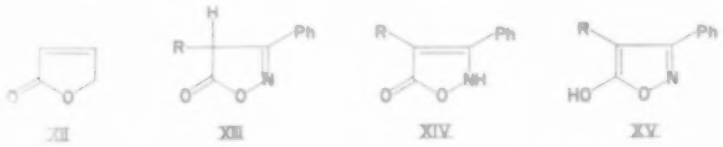
FIG. 1. Aqueous solutions; FIG. 2. Solutions in sulphuric acid.
——3,4-Dimethyl-5-hydroxyisoxazole; — — — — 3,4,4-Trimethylisoxazol-5-one;
× × × × 3,4-Dimethyl-5-methoxyisoxazole; · · · · · · · 2,3,4-Trimethylisoxazol-5-one.

holds for solutions in water (Fig. 1) and cyclohexane, and indicates that in both solvents the tautomeric compound exists predominantly in the hydroxy- form. The ultraviolet spectrum (Fig. 1) indicates that the proportion of the NH form does not exceed

1 per cent and that that of the CH form does not exceed 20 per cent and is probably much lower. The spectra of the mono-cations of the 3,4-dimethyl series are shown in Fig. 2. Three structures are possible for these cations, (IX–XI): 5-methoxy- com-

IX X XI

pounds must form cations of type IX, and 4,4-dimethyl- compounds must form cations of type X, but 2-methyl-, and potentially tautomeric compounds could form cations of all three types. Fig. 2 and Table 1 indicate that cations of structure IX are formed whenever possible; those of type XI should have U.V. spectra similar to XII, which shows only end absorbtion above 210 mμ in ethanol.[16]



XII XIII XIV XV

The spectra of aqueous solutions of neutral species in the 3-phenyl series are shown in Fig. 3, which indicates that 3-phenylisoxazol-5-one exists predominantly as the CH form (XIII, R = H) in equilibrium with ca. 30 ± 10 per cent of the NH form (XIV,

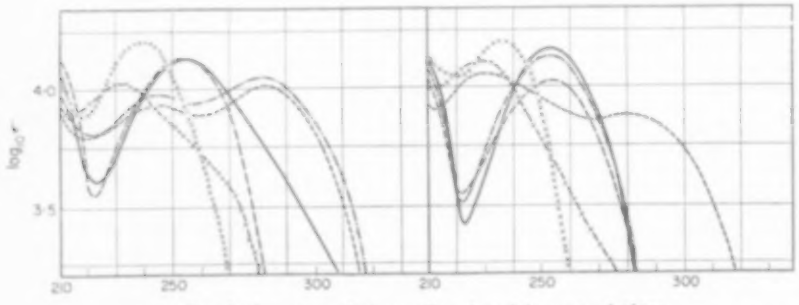


FIG. 3. Aqueous solutions; FIG. 4 cyclohexane solutions.
——3-Phenylisoxazol-5-one; — · — · —, 4-Methyl-3-phenylisoxazol-5-one; ——4,4-Dimethyl-3-phenylisoxazol-5-one; × × × × 5-Methoxy-3-phenylisoxazole; — × — × — 5-Methoxy-4-methyl-3-phenylisoxazole; · · · · · · 2, 4-Dimethyl-3-phenylisoxazol-5-one.

R = H); the OH form (XV, R = H) cannot be detected, its proportion is probably less than 10 per cent. 4-Methyl-3-phenylisoxazol-5-one, on the contrary, exists predominantly in the NH form (XIV, R = Me); no contributions from the other forms (XIII, XV, R = Me) can be detected; they probably occur to an extent of less than 10 per cent. However, in cyclohexane (Fig. 4) both the potentially tautomeric compounds exist predominantly in the CH form; Fig. 4 indicates that the NH and OH forms certainly do not exceed 10 per cent. Using cyclohexane, diethyl ether, ethanol

[16] R. J. D. Smith and R. N. Jones, *Canad. J. Chem.* **37**, 2092 (1959).

0·1 N sulphuric acid, and mixtures of adjacent pairs of these, solutions of each tautomeric compound in media of increasing polarity were prepared. 3-Phenylisoxazol-5-one shows a steady increase in the intensity of the NH peak with increasing solvent polarity, while with the 4-methyl homologue a gradual and apparently complete transition from CH to NH structure is observed (Figs. 5, 6).

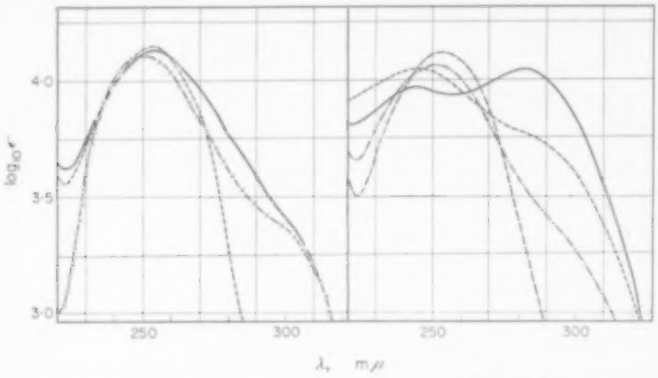


FIG. 5. 3-Phenylisoxazol-5-one; FIG. 6. 4-Methyl-3-phenylisoxazol-5-one.
——Aqueous sulphuric acid; —×—×—×— Ethanol–diethyl ether 1:1 + trace sulphuric acid; ····· Diethyl ether; —·—·—·— Cyclohexane–diethyl ether 1:1; — — — — Cyclohexane solution.

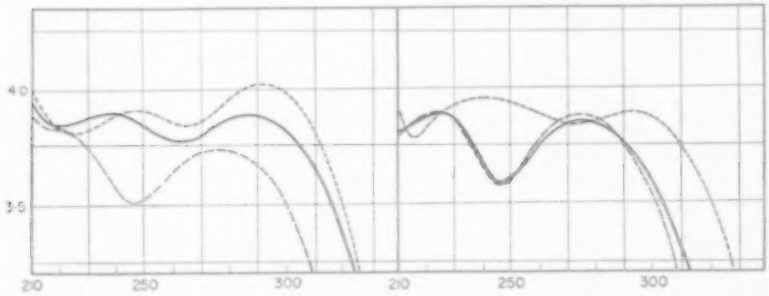


FIG. 7. Aqueous solutions; FIG. 8. Cyclohexane solutions.
——4-Bromo-3-phenylisoxazol-5-one; — — — — 4-Bromo-4-methyl-3-phenylisoxazol-5-one; ····· 4-Bromo-2-methyl-3-phenylisoxazol-5-one.

Considering the bromo-compounds of fixed structure, the expected bathochromic shifts of 3–11 mμ are found for 4-bromo-2-methyl-3-phenylisoxazol-5-one compared with the 2,4-dimethyl analogue in water and cyclohexane. More surprising are the larger shifts of 19–28 mμ for 4-bromo-4-methyl-3-phenylisoxazol-5-one compared with the 4,4-dimethyl analogue, and the second band found for the former compound above 210 mμ. This effect is presumably due to some specific interaction between the bromine atom and the phenyl ring (cf. Ref 17); the further large shift for the 4,4-dibromo-analogue (Table 1, No. 13) also indicates this. On the reasonable assumption that the spectrum of 4-bromo-5-methoxy-3-phenylisoxazole would be similar to that of its 4-methyl analogue, Figs. 7 and 8 show that 4-bromo-3-phenylisoxazol-5-one exists

[17] J. W. Smith and S. M. Walshaw, *J. Chem. Soc.* 3784 (1959).

predominantly as a mixture of CH and NH forms in aqueous solution but as the CH form in cyclohexane.

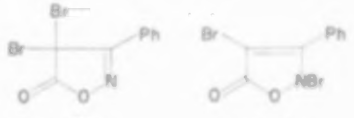
Infra-red spectra. Infra-red spectra demonstrate: (a) 5-hydroxy-3,4-dimethylisoxazole exists as such in the solid and in chloroform solution, (b) 3-phenylisoxazol-5-one exists in the CH form in the solid and chloroform,(c)4-methyl-3-phenylisoxazol-5-one exists as the NH form in the crystal, as a mixture (ca. 1:2) of NH and CH forms in chloroform, and mainly as the CH form in tetrachloroethylene, (d) 4-bromo-3-phenylisoxazol-5-one exists as the NH form in the solid but mainly as the CH form in $CHCl_3$ solution.

These conclusions were reached by comparing the detailed spectra of the potentially tautomeric compounds with those of known structure. The spectra of compounds of the isoxazole structure are discussed elsewhere;[6] those of 2H- and 4H-isoxazol-5-ones are recorded in Tables 2 and 3 respectively.

Some 2H-isoxazol-5-ones show νC=O absorption in chloroform as two partially resolved bands at 1740–1725 cm^{-1}; the cause of this splitting is not clear. The position is strongly dependent on the environment; in the less polar solvent C_2Cl_4, absorption is at ca. 1760 cm^{-1} and in the solid at ca. 1680 cm^{-1}. This behaviour is characteristic of a highly polarized C=O group.[18] The highest ring frequency, essentially νC=C, is shown as a strong band at 1645–1613 cm^{-1} (160–230) in solution and at somewhat lower frequencies in the solid phase. Four ring stretching modes and two C–H deformation modes are shown for the monosubstituted benzene rings as expected.[19] The 2H-isoxazol-5-one ring itself apparently absorbs (in addition to the νC=C band) at 1473–1463 cm^{-1} (35–50), 1377–1359 (25–70), 1296–1264 (10–45), 1197–1140 (35–60) and 1065–1036 (45–65), because these bands appear in all the compounds. Bands found only in the N—Me and others in the C—Me compounds, were assigned to corresponding modes as noted in Table 2.

4H-Isoxazol-5-ones show νC=O absorption at 1808–1793 cm^{-1} (410–600) except that the frequency is higher for Nos 5 and 13 with bromine α- to the C=O group. The highest ring frequency, essentially νC=N, absorbs at 1620 cm^{-1} (15) when not conjugated and at 1566–1553 cm^{-1} (15–30) when conjugated with a phenyl group. Other 4H-isoxazol-5-one ring bands are found at 1196–1151 cm^{-1} (70–170), 952–940 (5–25), and 900–872 (280–380). Most of the other bonds could be satisfactorily assigned to other structure groups within the various molecules as is briefly indicated in Table 3.

Dibromination of 3-phenylisoxazol-5-one yields a compound originally[15] for-



XVI XVII

mulated as the 4,4-dibromo-derivative (XVI). Subsequently, formula XVII was proposed[4] because the compound liberated one equivalent of iodide in neutral solution. The infra-red spectrum (Table 3, No. 9) clearly confirms the original formulation (XVI); the chemical evidence can be reconciled with this, for bromine in XVI would be expected to be more reactive than that in XIV, (R = Br).

[18] L. J. Bellamy and R. L. Williams, *Proc. Roy. Soc.* A **255**, 22 (1960).
[19] A. R. Katritzky and J. M. Lagowski, *J. Chem. Soc.* 4155 (1958).

VOL.
12
1961

TABLE 2. INFRA-RED SPECTRA OF 2H-I

No.	Substituents	Medium	Thickness mm	conc. M	νC=O		νC=C		Phenyl ring stretch				Isoxazolone ring		Phenyl νCC		N-Me CH-de	
					cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε
1	2,3,4-trimethyl	$CHCl_3$	0·1	0·2	1741* 1725	400 550	1645	200	—NA—		—NA—		—NA—		1473	35	—NA—	
2	2,4-dimethyl-3-phenyl	$CHCl_3$	0·1	0·2 0·05	1739 1725*	740 680	1635	230	1601	50	1578	20	1501	45	1468	50	1451*	80
3	2,4-dimethyl-3-phenyl	C_2Cl_4	0·1	0·05	1760	1200	1645	160[b]										
4	4-bromo-2-methyl-3-phenyl	$CHCl_3$	0·1	0·2 0·05	1749	1100	1614	110	1594	85	1575	85	1497	85	1471	35	1454	85
5	4-bromo-2-methyl-3-phenyl	C_2Cl_4	0·1	0·04	1769	1050	1613	130[b]										
6	4-methyl-3-phenyl	Nujol/HB	film	—	1694* 1677	*vs*	1611	*s*	1600*	*m*	1574	*m*	1501	*w*	1470	*m*	1450*	*w*
7	4-methyl-3-phenyl[a]	$CHCl_3$	0·1	0·2	1735	240	1639	70	1600	15	1579	10	1502†	15	(—)		1453†	60
8	4-bromo-3-phenyl	Nujol/HB	film	—	1688 1664*	*vs* *vs*	1560 1543*	*m*	1605	*w*	1584	*w*	1487	*m*	1463	*m*	1441	*w*

[a] Mixture of two tautomers. [b] not investigated at low wave numbers. * shoulder, † band considered to results from the superimposition of two peaks, —

TABLE 3. INFRA-RED SPECTRA OF 4H-ISO

No.	Substituents	Phase	Thickness mm	conc. M	νC=O		νC=N		Phenyl νCC		Phenyl νCC		CH def. and Ring mod			
					cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A
1	2,3,4,-trimethyl	$CHCl_3$	0·1	0·2	1793	440	1620	15	NA		NA		1470 1436	70 65	1394	70
2	4,4-dimethyl-3-phenyl	$CHCl_3$	0·1	0·2	1803	520	1562	30	1509	15	1452	50	1472	95	1397	70
3	3-phenyl	$CHCl_3$	0·1	0·2	1807	600	1566	30	1504	5	1452	55	—		1390*	55
4	3-phenyl	Nujol	film	—	1801	*vs*	1559	*m*	1593 1496	*w* *w*	1446	*m*	—		1382	*m*
5	4-bromo-3-phenyl[c]	$CHCl_3$	1[a]	0·02	1817	480	1555	15	($CHCl_3$)		1449	50	—		—	
6	4-methyl-3-phenyl	C_2Cl_4	1[a]		1808		—		1500		1451		—		—	
7	4-methyl-3-phenyl[b]	$CHCl_3$	0·1	0·2	1800	370	1564	20	1502†	15	1453†	60	—		—	
8	4-bromo-4-methyl-3-phenyl	$CHCl_3$	0·1	0·2	1805	470	1553	25	1503	10	1451	105	—		1384	55
9	4,4-dibromo-3-phenyl[d]	$CHCl_3$	0·1	0·2	1813	410	1554	25	1604 1500	15 15	1450	60	—		1358	65

[a] insufficiently soluble for 0·1 mm cells. [b] mixture of two tautomers. [c] Band at 1742 cm^{-1} (50) indicates small quantity of NH tautomer present.
* shoulder, † band considered to results from the superimposition of two peaks, — absence of band, (—) region masked by stronger absorption.

2H-ISOXAZOL-5-ONES

N-Me H-def		4-Me CH def		Isoxazolone ring			N-Me rock	Phenyl βCH	Isoxazolone ring	Phenyl βCH	?	N-Me ?	?
cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1} ε_A	cm^{-1} ε_A	cm^{-1} ε_A	cm^{-1} ε_A	cm^{-1} ε_A	cm^{-1} ε_A	cm^{-1} ε_A	cm^{-1} ε_A
00 75	1410	45 1393 45	1367 50	1296 40	1175 35	1126 145	—NA—	1045 45	—NA—	985 35	916 20	831 15
44 85	1419	20 1397 45	1377 70	1280 45	1152 60	1129 175	—	1065 55	1039 50	1006 55	922 25	860 40
13 50	—NA—	—NA—	1365 25	1290 10	1192 30 1140 25	1114 140	1077 10	1041 65	1025 10	988 120	925 10	850 25
NA—	—	1394 *w*	1377 *w*	1290 *w* 1240 *w*	1190 *w*	—NA—	1079 *m*	1057 *w*	1028 *w*	1001 *m* 988 *m*	—NA—	890 *w*
NA—	1410	25 1387† 50	1364 25	1264 35	(—)	—NA—	(—)	1062 50	1021 30	1000 55 990 60	—NA—	—
NA—	—NA—	—NA—	1359 *w*	—	1197 *w* 1153 *w*	—NA—	1075 *w*	1036 *m*	1027* *w*	993 *m* 987 *m* 967 *w*	—NA—	—

ks, — absence of band, (—) region masked by stronger absorption.

H-ISOXAZOL-5-ONES.

modes		isoxazolone ring		?	4-Me rocking	Phenyl βCH	Isoxa-zolone ring	?	Isoxa-zolone ring	Phenyl	Isoxa-zolone ring	?
cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1} ε_A	cm^{-1} ε_A	cm^{-1} ε_A	cm^{-1} ε_A	cm^{-1} ε_A	cm^{-1} ε_A	cm^{-1} ε_A	cm^{-1} ε_A	cm^{-1} ε_A
1370	15	1160	130	(—)	1267 65 1116 150	—NA—	1001 65	(—)	952 20	—NA—	872 300	—
1375 20 1357 30		1196 70 1186 60		1001* 90	1253 50 1114 160	1076 40	1011 10	999 5	947 25	918 20	888 360	—
1370	100	1166	170	1099 10	—NA—	1074 30	1043 35	996 5	940 5	914 25	892* 190 876 280	845* 30
1360 *m* 1315 *w*		1160	*vs*	1105 *w*	—NA—	1077 *m*	1043 *m*	996 *w*	943 *w*	917 *m*	900 *s* 875 *s*	849* *m*
1367 90 1335 15		1151	110	1125 45 1098 20	—NA—	1073 25	1050 10	—	940* 10	(—)	886 280 861 120	844* 80
1385							hidden by solvent					
1387† 50		1168	100	1101 15	1091 20	(—)	1038 40	(—)	—	918 10	883 270	829 5
1357	55	1158 65 1162* 50		(—)	1086 140	1073* 100	1042 50	1010 30	—	920 15	887 380	837 15
1336 40 1315 10		1158	200	1099 40	—NA—	1071 20 1025 10	—	1000 5	942 190[e]	922 30	897 280 866 200	830 60 812 65

t. [d] prominent overtones at 1885 cm^{-1} (25), 1836* (105), and 1755* (20). [e] possibly this high intensity is connected with the CBr_2 group.

VOL
13
196

The infra-red spectrum of 3,4-diphenylisoxazol-5-one (KBr disk) has been published by Scarpati and Speroni[20]. A very strong band at ca. 1680, with a shoulder at ca. 1690 cm^{-1} and other bands at ca. 1600 (s), 1470 (m), 1340 (w), 1070 (w) and 990 cm^{-1} (w) show that this compound exists in the NH form in the crystalline phase and not the CH as earlier supposed.[3] The absence of strong absorption near 1800 and 880 cm^{-1} supports our conclusion.

Basicity determinations. Difficulty was encountered in applying the basicity method to the determination of tautomeric ratios in this series. Titration in aqueous

TABLE 4. BASE STRENGTHS OF ISOXAZOLES (pK_a OF CONJUGATE ACID)

	0·2 M solution[a]	0·38 M solution[a]	indicator[b]
Isoxazole	−1·96 ± 0·04	−2·28 ± 0·02	A
3-Methylisoxazole	−1·76 ± 0·02	−1·92 ± 0·03	A and B
5-Methylisoxazole	−1·72 ± 0·01	−1·95 ± 0·05	A and B
3,5-Dimethylisoxazole	−1·27 ± 0·02	−1·28 ± 0·02	B
3,4-Dimethyl-5-methoxy-isoxazole	−1·47 ± 0·01	−1·56[c]	B
2,3,4-Trimethylisoxazol-5-one	−1·24 ± 0·01	−1·32[c]	B
3,4-Dimethyl-5-hydroxyisoxazole	−0·66[c]	—	B

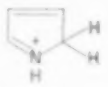
[a] Means of 3 or 4 determinations, and standard deviation of the mean.
[b] B represents 4-chloro-2-nitro-N-methylaniline, pK_a −1·37.[21] A represents N-(2′,4′-dinitrophenyl) morpholine, pK_a −2·21, which was determined by the spectrophotometric method using B as standard.
[c] Single readings, estimated errors 0·05.

solution could not be used as the basicities were too low. Usually the spectrophotometric method was inapplicable because of insufficient difference between the spectrum of the base and cation. Titration in non-aqueous solvents was avoided on account of the difficulties in relating the results to aqueous solutions. The indicator method of Lemaire and Lucas[21] was used: it consists in preparing a solution in acetic acid of the base together with half an equivalent of a strong acid. If the compound is considerably more basic than the solvent, the solution contains equal amounts of the base and its conjugate acid; if activities may be equated, then the acidity of the solution is equal to the pK_a of the base. Addition of a known small amount of a suitable indicator allows the determination of the acidity of the solution using the indicator spectrum. It was difficult to prepare solutions of perchloric acid in acetic acid free both from acetic anhydride (a powerful acetylating agent) and from water; therefore, sulphuric acid, treated as a monobasic acid, was used. (Some determinations were made in nitromethane in place of acetic acid, but concentration effects were found to be much greater). The values obtained (Table 4) varied with concentration, but values at the same concentration should be comparable. In the case of 2,3,4-trimethylisoxazolone, a value of $-1{\cdot}58 \pm {\cdot}01$ was obtained by the spectrophotometric method ($1{\cdot}3 \times 10^{-3}$ M); this is in reasonable agreement with the results in Table 4.

As no base strengths of simple isoxazoles appear to have been reported, isoxazole and some methyl derivatives were measured. Isoxazole is a base of approximately the same strength as water (pK_a −2·35).[21] Substituting —O— for an adjacent —CH=CH— in pyridine thus lowers the basicity of the nitrogen atom by ca. 7 pK

[20] R. Scarpati and G. Speroni, *Gazz. Chim. Ital.* **89**, 1511 (1959).
[21] H. Lemaire and H. J. Lucas, *J. Amer. Chem. Soc.* **73**, 5198 (1951).

units. Isoxazole is a weaker base than pyrrole (pK_a −0·27)[22] although the aromaticity of pyrrole is destroyed on cation formation (XVIII)[23] but not that of isoxazole (cf.



XVIII

XIX

XIX). Methyl groups raise the basicity of isoxazole by ·2–·5 units, as expected. However, the basicity of 5-hydroxy-3,4-dimethylisoxazole is lowered ·8 unit by O-methylation and ·6 unit by N-methylation. This result is unexpected, as is the small difference between the basicities of the two methyl derivatives in view of the large preference for the hydroxy-form shown by 5-hydroxy-3,4-dimethylisoxazole.

TABLE 5. ACID STRENGTHS OF ISOXAZOLONES IN AQUEOUS SOLUTION

3-Substituent	Me	Ph	Ph	Ph
4-Substituent	Me	H	Me	Br
pK	6·1	4·01	4·73	2·3
Standard deviation	0·15	0·02	0·02	0·1
Method	potentiometric titration	spectrophotometric		

TABLE 6. THE TAUTOMERIC NATURE OF ISOXAZOL-5-ONES

Substituents at positions		Cyclohexane solution	Tetrachloroethylene solution	Chloroform solution	Aqueous solution	Solid state
3	4	(UV)	(IR)	(IR)	(UV)	(IR)
Me	Me	>80% OH	—	>98% OH	>80% OH	OH
Ph	H	>90% CH	—	>98% CH	70% CH + 30% NH	CH
Ph	Me	>90% CH	90% CH + 10% NH	70% CH + 30% NH	>90% NH	NH
Ph	Br	>90% CH	>95% CH	90% CH + 10% NH	20% CH + 80% NH	NH

The measured pK values for the isoxazolones as acids are recorded in Table 5; considered as analogues of phenol (pK 9·95) they are remarkably strong acids, comparable with carboxylic acids. In 1892, Hantzsch and Miolati[24] found pK 4·27 for 3-phenyloxazol-5-one by a conductivity method.

Conclusions. The results of this investigation are summarized in Table 6. Obviously, the balance between the various tautomers is a delicate one, and may depend on mesomeric, inductive, and steric effects. It is not possible to generalize on the basis of the four compounds so far studied: further work is in hand.

EXPERIMENTAL

Petroleum ether refers to the fraction of b.p. 60–80°, unless otherwise specified.

5-Hydroxy-3,4-Dimethylisoxazole.[1] This was crystallized from water and sublimed at 125° 0·1 mm and had m.p. 125–126° (lit.[1] m.p. 123–124°).

3,4-Dimethyl-5-methoxyisoxazole. Ethereal diazomethane (ca. 0·6 g) was added to 5-hydroxy-3,4-dimethylisoxazole (2·0 g) until the yellow colour persisted. After 5 min, the ethereal solution was

[22] N. Naqvi and Q. Fernando, *J. Org. Chem.* **25,** 551 (1960).
[23] R. J. Abraham, E. Bullock and S. S. Mitra, *Canad. J. Chem.* **37,** 1859 (1959).
[24] A. Hantzsch and A. Miolati, *Z. Phys. Chem.* (*Leipzig*) **10,** 19 (1892).

shaken successively with 2 N HCl (10 cc) and 2 N NaOH (10 cc), dried ($MgSO_4$) and distilled to give the *isoxazole* (1·1 g, 50%) b.p. 100° (bath)/15 mm, which formed prisms (from petroleum ether) m.p. 32–34° (Found: C, 56·5; H, 7·5; N, 10·6; MeO, 23·5. $C_6H_9NO_2$ requires: C, 56·7; H, 7·1; N, 11·0; MeO, 24·4%).

The neutral silver salt[1] of 5-hydroxy-3,4-dimethylisoxazole (1·6 g) was refluxed for 2 hr in ethanol (10 cc) with methyl iodide (1·5 g). After filtration, solvent was removed from the filtrate and ether (20 cc) added to the residue. The solution was extracted with 0·1 N NaOH (2 × 20 cc), dried ($MgSO_4$) and evaporated, to give an oil (0·3 g), shown to be crude methoxy- compound by the infra-red spectrum. The same methoxy-compound (ca. 10%) was also obtained by treatment of 5-hydroxy-3,4-dimethylisoxazole with methyl iodide and sodium ethoxide as in the preparation of 2,4-dimethyl-3-phenylisoxazol-5-one.

5-Methoxy-3,4-dimethylisoxazole in dil ethanol gave a *cadmium chloride complex* on mixing with saturated aqueous cadmium chloride, which crystallized as needles (Found: C, 22·4; H, 3·7; N, 4·4. $C_6H_9NO_2{\cdot}CdCl_2{\cdot}H_2O$ requires: C, 21·9; H, 3·4; N, 4·2%).

3,4-*Dimethyl*-5-*ethoxyisoxazole*. Diazoethane and 5-hydroxy-3,4-dimethylisoxazole gave the ethoxy-compound (80%), b.p. 110° (bath)/15 mm (Found: C, 59·6; H, 8·1; N, 9·4; $C_7H_{11}NO_2$ requires: C, 59·6; H, 7·9; N, 9·9%).

2,3,4-*Trimethylisoxazol*-5-*one*. N-Methylhydroxylamine[7] (16 g) in ethanol (40 cc) was added during ½ hr to ethyl methylacetoacetate (48 g) in ethanol (100 cc) and acetic acid (1 cc) at 25°. The whole was refluxed 4 hr and then distilled. Redistillation of the fraction of b.p. 148–151°/15 mm gave the *isoxazolone* (30·1 g, 68%), b.p. 108°/2 mm, which crystallized from benzene–petroleum ether (ca. 1 : 1) as prisms, m.p. 36° (Found: C, 5·70; H, 7·4; N, 10·8%).

3,4,4-*Trimethylisoxazol*-5-*one*. prepared by Billon's method,[9] had b.p. 101–102°/15 mm, n_D^{24} 1·4393 (lit.[9] b.p. 102–103°/15 mm).

3-*Phenylisoxazol*-5-*one*.[10] This formed plates, m.p. 151–153° (decomp) from chloroform (lit.[4] m.p. 151–152°).

4-*Methyl*-3-*phenylisoxazol*-5-*one*[11] had m.p. 121–122° (lit.[11] m.p. 123–124°).

4,4-*Dimethyl*-3-*phenylisoxazol*-5-*one*. Ethyl benzoyldimethylacetate (8·4 g), hydroxylamine hydrochloride (5 g), sodium acetate (1 g), water (15 cc) and ethanol (70 cc) were refluxed 3 hr, 12 N HCl (5 cc) was then added and the whole refluxed 30 min more. Volatile matter was removed to 80°/15 mm, water (20 cc) was added, and the mixture ether-extracted (2 × 20 cc). Evaporation of the dried ($MgSO_4$) extracts, and crystallization of the residue from ether, gave the isoxazolone (4·4 g, 61%) which sublimed at 100°/0·1 mm, m.p. 70° (lit.[11] m.p. 70–71°).

5-*Methoxy*-3-*phenylisoxazole*. Prepared from 3-phenylisoxazol-5-one and diazomethane,[12] this compound (m.p. 76–77° after 2 crystallizations from light petroleum) was identical with a sample prepared from the isoxazolone using methanol and sulphuric acid[1] (m.p. 77–78·5° after similar treatment), by the infra-red spectra. (Found: MeO, 16·7; Calc. for $C_{10}H_9NO_2$: MeO, 17·7%).

Treatment of 3-phenylisoxazol-5-one with methyl iodide and sodium ethoxide, as in the preparation of 2,4-dimethyl-3-phenylisoxazol-5-one, gave a viscous oil (80%) which did not solidify in 3 weeks. The infra-red spectrum showed that it contained 2-methyl-3-phenylisoxazol-5-one and 5-methoxy-3-phenylisoxazole in a proportion of ca. 9 : 1.

2,4-*Dimethyl*-3-*phenylisoxazol*-5-*one*. Methyl iodide (16 g, 7·0 cc) was added to 4-methyl-3-phenylisoxazol-5-one (17·5 g) in ethanolic sodium ethoxide (from 2·5 g Na and 150 cc EtOH) and the whole refluxed in 1½ hr. Ethanolic sodium ethoxide (from 2 g Na and 40 cc EtOH) and methyl iodide (12 g, 5·3 cc) were then added and refluxing continued for 1½ hr more. Volatile matter was removed to ca. 80°/15 mm, water (50 cc) added, and the whole ether-extracted (2 × 40 cc). The ethereal extracts were shaken with 2 N NaOH (50 cc), dried ($MgSO_4$) and the ether evaporated to give the *isoxazolone* (13·8 g, 73%), which separated as needles from benzene–petroleum ether (ca. 1 : 2), m.p. 66·5–67·5° after 3 crystallizations and sublimation at 80°/0·05 mm (Found: C, 70·3; H, 6·2; N, 7·4; OMe, 0·0. $C_{11}H_{11}NO_2$ requires: C, 69·8; H, 6·2; N, 7·4%).

5-*Methoxy*-4-*methyl*-3-*phenylisoxazole*. Diazomethane (ca. 1·0 g in ether) was added to a suspension of 4-methyl-3-phenylisoxazol-5-one (4·0 g) in ether (60 cc). The ethereal solution was then shaken with 2 N HCl (20 cc) and 2 N NaOH, (50 cc), the ether evaporated and the residue distilled 3 times (bath 105°; 0·05 mm) and crystallized from light petroleum (b.p. 40–60°). The *methoxy-compound* (0·1 g; 2·5%) had m.p. 30–32° (Found: C, 70·0; H, 6·5; N, 7·3%).

4-*Bromo*-2-*methyl*-3-*phenylisoxazol*-5-*one*. 4-Bromo-3-phenylisoxazol-5-one[14] (m.p. 120–121°

0·3 g; lit.[14] m.p. 121–122°) in ethanol (20 cc), treated with ethereal diazomethane (ca. 0·05 g), gave on evaporation of the solvents the N-*methyl derivative*, as needles (0·15 g, 48%), m.p. 106–107°, from ether–pet ether (ca. 1 : 2) (Found: C, 47·2; H, 3·3; N, 5·6. $C_{10}H_8BrNO_2$ requires: C, 47·2; H, 3·2; N, 5·5%).

4-*Bromo*-4-*methyl*-3-*phenylisoxazol*-5-*one*. Bromine (2·9 g) in chloroform (20 cc) was added over 5 min to 4-methyl-3-phenyl-5-isoxazolone (3·0 g) in chloroform (50 cc). The mixture was warmed to 50° for 10 min and the chloroform removed under reduced press. The residual *isoxazolone*, crystallized twice from petroleum ether, had m.p. 42–43° (3·1 g, 71%) (Found: C, 47·5; H, 3·5; N, 6·0%).

4,4-*Dibromo*-3-*phenylisoxazol*-5-*one*. This was prepared by the method of Meyer,[15] and had m.p. 76·5–77° (lit.[15] m.p. 76–77°).

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VOL. 12 1961

THE TAUTOMERISM OF HETEROAROMATIC COMPOUNDS WITH FIVE-MEMBERED RINGS—II[1]

3-,4- AND 5-AMINO- AND ACETAMIDO-ISOXAZOLES

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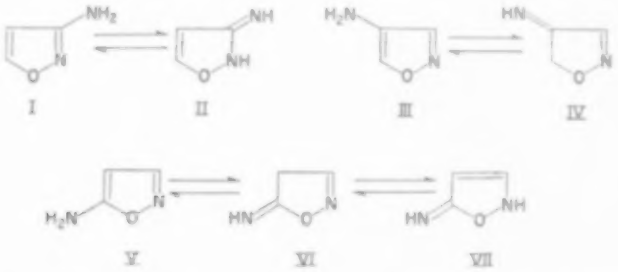
(*Received* 23 *August* 1960)

Abstract—Infra-red and nuclear magnetic resonance spectra show that all types of amino- and acetamido-isoxazoles exist predominantly as such.

Ultra-violet spectroscopy indicates that 3- and 5-amino-isoxazoles are protonated at the ring nitrogen atom, but the 4-amino- analogues on the amino- group. Basicities of these compounds are recorded.

ALL amino-isoxazoles are potentially tautomeric: 3- (I) and 4-amino-compounds (III) are each in equilibrium with one imino-form, II and IV respectively, and 5-amino-compounds (V) are in equilibrium with two imino-forms VI and VII. These possibilities have long been realized—in Beilstein the compounds are classified as imino-derivatives of the corresponding isoxazolones[2]—but little definitive evidence as to the predominating structures is available. For the 5-series, v. Auwers *et al.* argued that chemical evidence favoured the amino-structure (V) rather than the imino- (VI) [imino-forms of type VII were apparently not considered] for the 3-phenyl[3] and 3,4-tetramethylene compounds.[4] Physical methods have not been applied up to now, with the exception of molecular exaltation which did not provide clear-cut evidence.[3,4] Acetamido-isoxazoles could show tautomerism in an exactly analogous way to the amino-compounds.



Following our work on potential 5-hydroxyisoxazoles, we have now investigated typical amino- and acetamido-compounds of each type. Compounds were prepared by known methods (see Tables 1 and 2). Attempted reduction to the amine of 20 g of

[1] Part I: *Tetrahedron* **12**, 41 (1961).
[2] *Beilstein, Hauptwerk* **27**, *inter alia*, pp. 157, 200.
[3] K. v. Auwers and H. Wunderling, *Ber. Dtsch. Chem. Ges.* **67**, 638 (1934).
[4] K. v. Auwers, T. Bahr and E. Frese, *Liebigs Ann.* **441**, 68 (1925).

4-nitro-3,5-dimethylisoxazole with stannous chloride became uncontrollably violent (cf. ref. 5), but amalgamated aluminium foil in moist ether was satisfactory.[6]

Infra-red spectra. An investigation of the spectra of many substituted isoxazoles showed that all bands of appreciable intensity could be assigned to the substituents or to the isoxazole ring.[7] All the amino- and acetamido-isoxazoles presently studied showed the characteristic ring bands[7] and all other bands ($\varepsilon_A > 10$) could be assigned to the amino- (Table 1), acetamido- (Table 2), or other substituents.[7] Spectra of 0·185 M chloroform solutions were measured in 0·108 mm cells and apparent extinction coefficients are recorded.[7]

TABLE 1. INFRA-RED SPECTRA OF AMINO-ISOXAZOLES

Substituents			1	2	3	4	5	6	7	lit.
			N—H stretch		NH_2 scissor and 1st ring mode		νC—N	m.p.	lit. m.p.	ref. 8
3	4	5	asym	sym						
			cm^{-1} ε_A	cm^{-1} ε_A	cm^{-1} ε_A	cm^{-1} ε_A	cm^{-1} ε_A			
NH_2	—	Me	3450 35	3370 40	1629 380	1612[a]	1278 85	61–62°	61–62°	11
NH_2	—	Et	3480 40	3385 45	1627 420	(–)	1302 10	64–66	64–66	12
NH_2	—	Ph[a]	3455 40	3370 50	1629 330	1614[a] 140	1269 20	137–138	139–139·5	12
Me	NH_2	Me	3410 20	3345 15	1660 70	1612 40	1272 25	54·5–56	56–57	6
Me	—	NH_2	3490 60	3395 75	1636 530	1590 65	1333 10	85–86	86	13
Me	Me	NH_2	3455 45	3360 65	1658 440	1600 105	1240 65 1327 10	121–122·5	125	14
Ph	—	NH_2	3465 55	3365 85	1635 630	(–)	1335 15 1310 10 1285 10	111–113	110–112	15, 13

[a] additional bands found at 1056 (35), 942 (60).

The amino- compounds all show two bands in the NH stretching region, at 3485–3390 cm^{-1} (20–65) and 3390–3330 cm^{-1} (15–85) (Table 1, cols. 1 and 2). If the 4- and 5-amino- compounds existed in 5H-isoxazol-4-onimine (IV) and 4H-isoxazol-5-onimine forms (VI), respectively, the two bands in the NH region would have to be assigned to hydrogen-bonded and free molecules. This possibility was excluded by showing that the relative intensities of the two bands were unchanged for 4-amino-3,5-dimethyl and 5-amino-3-methyl isoxazole in 0·02 M solutions in 1 mm cells. If the 3- and 5-amino-compounds existed in 2H-isoxazol-3-onimine (II) and -5-onimine forms (VII), respectively, one of the two bands in the νNH region would be due to the hydrogen attached to the cyclic nitrogen and the other to that attached to the exocyclic nitrogen. This possibility was excluded by deuteration experiments. When 3-amino-5-phenyl and 5-amino-3-methyl isoxazole were separately dissolved in deuterium oxide and the compound crystallized out or the solvent evaporated, the hydrogen attached to nitrogen was replaced by deuterium to an extent, under the conditions used, of roughly

[5] R. Justoni, *Gazz. Chim. Ital.* **70,** 802 (1940).
[6] G. T. Morgan and H. Burgess, *J. Chem. Soc.* **119,** 699 (1921).
[7] A. R. Katritzky and A. J. Boulton, *Spectrochim. Acta* In press.
[8] A. R. Katritzky and R. A. Jones, *J. Chem. Soc.* 3674 (1959).
[9] A. R. Katritzky and R. A. Jones, *J. Chem. Soc.* 2067, (1959).
[10] A. R. Katritzky and J. M. Lagowski, Review in preparation.
[11] H. Kano and K. Ogata, *Ann. Rep. Shionogi Res. Lab.* **7,** 1 (1957); *Chem. Abstr.* **51,** 17889 (1957).
[12] H. Kano, Personal communication.
[13] P. S. Burns, *J. Prakt. Chem.* **47,** 105 (1893).
[14] H. M. Wuest and M. Hoffer, U.S.Pat. 2,430,094; *Chem. Abstr.* **42,** 1610 (1948).
[15] A. Obrégia, *Liebigs Ann.* **266,** 324 (1891).
[16] H. Kano, *J. Pharm. Soc. Japan* **72,** 1118 (1952).

VOL. 12 1961

TABLE 2. INFRA-RED SPECTRA OF ACETAMIDOISOXAZOLES

Substituents 3	4	5	1 νN—H at 0·02 M cm⁻¹	ε_A	2 νN—H free cm⁻¹	ε_A	3 νN—H H-bonded cm⁻¹	ε_A	4 νC=O cm⁻¹	ε_A	5 Amide II cm⁻¹	ε_A	6 CH def. $COCH_3$ cm⁻¹	ε_A	7 νC—N cm⁻¹	ε_A	8 νC—N cm⁻¹	ε_A	m.p.	lit. m.p.	lit. ref.
NHAc	—	Me	3395	60	3395	25	3250*	70	1705	360	1560	160	1381	70	—		1280	250	185[c]	185[f]	11
							3215	85			1539*	140	1371	55							
							3140	65													
							3085	85													
Me	NHAc	Me	3410	55	3410	45	3270	45	1691	290	1515	110	1374	70	1325	15	1250	150	108–109	108–109	6
															1280*	40					
Me	—	NHAc[a]			3400	m	3250*		1715	vs	1548*	s	1372	m	—		1262	ms	174–175·5	169	13
							3210	w			1525	vs									
							3140	w													
Me	Me	NHAc			3390	50	3225	55	1710	310	1515*	180	1376	110	1309	70	1236	150	115–116	114–115	16
							3160*				1506	200									
Ph	—	NHAc			3380	55	3250*	20	1717	185	1546*	160	1370	45	—		1266	130	163–164	164	13
							3200	25			1516	350									

[a] saturated solution in chloroform.

80 per cent , as evidenced by infra-red intensities. For 80 per cent exchange the proportion of ND_2:NHD:NH_2 molecules would be 64:32:4. Bands due to ND_2 and NHD molecules could be clearly distinguished:-

Substituent	NHD	ND_2	NHD	ND_2
3 4 5	*ν*N—H cm^{-1}	*asym ν*N—D cm^{-1}	*ν*N—D cm^{-1}	*sym ν*N—D cm^{-1}
NH_2 — Ph	3410	2580	2525	2480
Me — NH_2	3445	2605	2540	2500 2470

The bands due to the NHD groups absorb at frequencies between those of the NH_2 and ND_2 groups respectively, this proves that the two hydrogen atoms are similarly placed; for the alternative possibilities mentioned above no distinct bands for NHD molecules would be found.

For aromatic amines, the position of each *ν*N—H band rises as the attached ring becomes more electron accepting; the apparent extinction coefficients also increase, that of the symmetrical vibration the more markedly.[8] The mean frequencies indicate that the 3- and 5-positions of the ring accept electrons much more readily than the 4-position. The mean intensities are in the order $4 < 3 < 5$ and the variation is greater for the symmetrical mode; however, the intensities for the 3-amino- compounds are probably lowered by intramolecular hydrogen bonding (cf. 2-amino-pyridine),[8] these results are thus not inconsistent with the frequency variation.

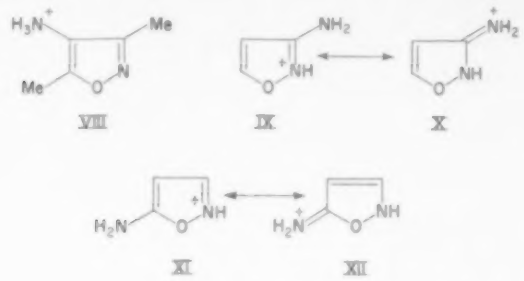
The amino- compounds usually show two bands in the 1600 cm^{-1} region (Table 1, cols. 3 and 4) which are attributed to the NH_2 scissor and a nuclear mode of the isoxazole ring.[7] However, the frequency and intensity of the ring mode in the deuterated compounds show that the two modes in the non-deuterated compounds can become highly mixed.

A weak to medium band in the 1330–1240 cm^{-1} region is presumably the *ν*C—N mode[8] (Table 1, col. 5). The other bands ($\varepsilon_A > 10$) could, with few exceptions given a footnote, be assigned to the ring or other substituent(s).

The NH-stretching region of the spectrum is complex for the acetamido- compounds in 0·2 M solution (Table 2, cols. 2, 3), but examination of 0·02 M solutions (Table 2, col. 1) shows that one band is due to free *ν*NH and the others to intermolecular hydrogen bonded *ν*NH, as is often found.[9] All compounds show the *ν*C=O, Amide II, and other bands associated with the acetamido- group;[9] the overall spectra afford strong evidence that these compounds exist predominantly in the acetamido- forms.

Ultra-violet spectra of neutral amino-isoxazoles and their cations in aqueous solution are recorded in Table 3. The 4-aminoisoxazole cation has a spectrum resembling that of 3,5-dimethylisoxazole (λ_{max} 214 mμ), showing its structure to be VIII; the bathochromic shifts which occur on cation formation by 3- and 5-amino-isoxazoles show that their structures are of the IX–X and XI–XII type respectively.

Basicities (Table 3). 4-Amino-3,5-dimethylisoxazole is a base considerably weaker than aniline ($pK_a = 4{\cdot}58$) showing that the isoxazole ring even at the 4-position is more electron accepting than the phenyl. Amino groups in the 3- or 5-positions



VIII IX X

XI XII

increase the basicity of isoxazoles[1] by ca. 2·5 pK units; for comparison, 2- and 4-amino-groups increase the basicity of pyridine by 1·7 and 4·0 pK units, respectively.

*Nuclear magnetic resonance spectra.** The N.M.R. spectra of 4-amino-3,5-dimethyl- and 5-amino-3,4-dimethyl-isoxazole were examined in aqueous and chloroform solutions. The two methyl groups of the 4-amino- compound showed as sharp absorption bands at chemical shifts (τ values) of 7·84 and 7·91 in water,† and at 7·90

TABLE 3. THE ULTRA-VIOLET SPECTRA AND BASICITIES OF AMINOISOXAZOLES

Substituent at positions			1		2		3		4
			Cyclohexane		Solvent water		2 N H_2SO_4		
3	4	5	λ(mμ)	ε	λ(mμ)	ε	λ(mμ)	ε	pK_a
NH_2	H	Me	—		209	6820	230	8040	0·47 ± 0·02[a]
Me	NH_2	Me	239	3020	242	3760	212	4710	3·8 ± 0·1[b]
Me	H	NH_2	227	4820	239	9210	254	12,200	0·64 ± 0·01[a]
Me	Me	NH_2	233	6380	244	8230	263	13,800	1·16 ± 0·01[a]

[a] Measured by the spectrophotometric method;
[b] by the titration method (estimated standard deviation of a single reading).

and 8·00 in chloroform, and those of the 5-amino- compound at 7·94 and 8·36 in water,† 7·97 and 8·35 in chloroform. The amino- groups gave broad bands in the chloroform solutions, the 4-amino- group at 7·32, the 5-amino- at 5·37 p.p.m. In each case the aminoisoxazole rather than the isoxazolonimine structure IV or VI was shown by the absence of splitting of either of the resonances due to the methyl groups, and by the absence of absorption attributable to a lone proton α to a methyl group.

General conclusions. It appears to be a general feature of tautomerism in heterocyclic compounds that the tendency for amino- compounds to exist as such is considerably greater than that for the hydroxy-analogues.[10] As there is little difference between the stabilities of the various tautomers for 5-hydroxyisoxazoles,[1] it is then not unexpected that 5-aminoisoxazoles exist in the amino-form.

Acknowledgement—We are very grateful to Dr. H. Kano for kindly providing specimens of the 3-aminoisoxazoles.

* These spectra were obtained using a Varian Associates 4300B spectrometer and 12" electromagnet, at 40 Mc/s, with flux stabilisation and sample spinning. The chemical shifts are quoted in parts per million on the silicon tetramethyl (τ) scale.

† measured using t-butanol (τ = +8·78) as internal standard.

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STUDIES IN THE SPHINGOLIPIDS SERIES—XVII*

SYNTHESIS AND RESOLUTION OF ERYTHRO AND THREO-C_{20}-DIHYDROSPHINGOSINES†

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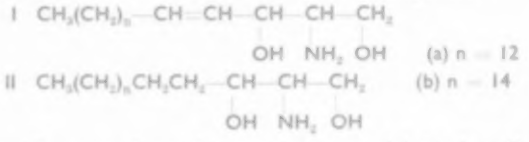
(*Received* 25 *July* 1960)

Abstract—Erythro and threo-1,3-dihydroxy-2-amino-eicosane have been obtained by addition of nitroethanol to octadecanal and subsequent reduction of both erythro and threo-nitrodiols. Resolution with L-glutamic acid gave four optically active forms of the base. The D-configuration has been assigned to the +-erythro-isomer.

SPHINGOSINE (Ia) is one of the eight stereoisomeric 1,3-dihydroxy-2-amino-4-octadecenes. Its saturated derivative, dihydrosphingosine (IIa), is one of the four possible isomers and has a structure of D+-erythro-1,3-dihydroxy-2-amino-octadecane. Both bases have been found in animal tissue and all stereoisomeric forms have been prepared synthetically.[1] Recently, we have discovered the third base of animal origin, C_{20}-sphingosine, which was isolated from horse and beef brain.[2] The new base has been characterized as 1,3-dihydroxy-2-amino-4-eicosene (Ib). So far there is no experimental evidence as to the stereochemistry of the C_{20}-base.



In continuation of our work on the new base we wish to describe first a synthesis of the four optically active forms of its dihydro derivative, C_{20}-dihydrosphingosine (IIb). This problem is of interest for several reasons. First, it is reasonable to suppose the occurrence of C_{20}-dihydrosphingosine in nature through analogy with C_{18}-dihydrosphingosine. On the other hand, the knowledge of the optical isomers of the dihydro base may offer an additional approach to the stereochemistry of the C_{20}-bases.

Of the many syntheses of C_{18}-sphingosine and C_{18}-dihydrosphingosine reported within the past few years the most practical appear to be those of Grob *et al.*[3,4] They consist in the first stage in the reaction of hexadecen-2-al-1 and hexadecanal-1 respectively with nitroethanol. Similar reaction scheme for the synthesis of C_{18}-dihydrosphingosine was proposed some twenty years ago by Seydel[5].

* Part XVI, see reference 2.

† Presented at the I. Congress of Pure and Applied Chemistry of Yugoslavia. Abstracts of papers, p. 131. Zagreb-Rijeka-Beograd, June (1960).

‡ Taken from a thesis by Mrs. B. Majhofer-Oreščanin in partial fulfillment for the Ph.D. University of Zagreb (1960).

[1] For recent reviews covering this field see H. E. Carter *et al.*, *Canad. J. Biochem. Physiol.* **34**, 320 (1956); *Fed. Proc.* **16**, 817 (1957).

[2] M. Prošteník and B. Majhofer-Oreščanin, *Naturwiss.* **47**, In press (1960).

[3] C. A. Grob, E. F. Jenny and H. Utzinger, *Helv. Chim. Acta* **34**, 2249 (1951).

[4] C. A. Grob and F. Gadient, *Helv. Chim. Acta* **40**, 1145 (1957).

[5] P. V. Seydel, *Zur Kenntnis des Sphingosins* Ph.D. Thesis, Zürich (1941).

In the present work the synthesis of the four 1,3-dihydroxy-2-aminoeicosanes (IIb) was carried out by the route indicated in Chart 1. The starting material was octadecanal-1 which was prepared in 66 per cent yield by the Rosenmund reduction of stearoyl chloride. Addition of nitroethanol to the aldehyde thus obtained in the presence of potassium carbonate furnished a mixture of DL-erythro- and DL-threo-1,3-dihydroxy-2-nitroeicosanes. Both nitrodiols A and B could easily be separated due to

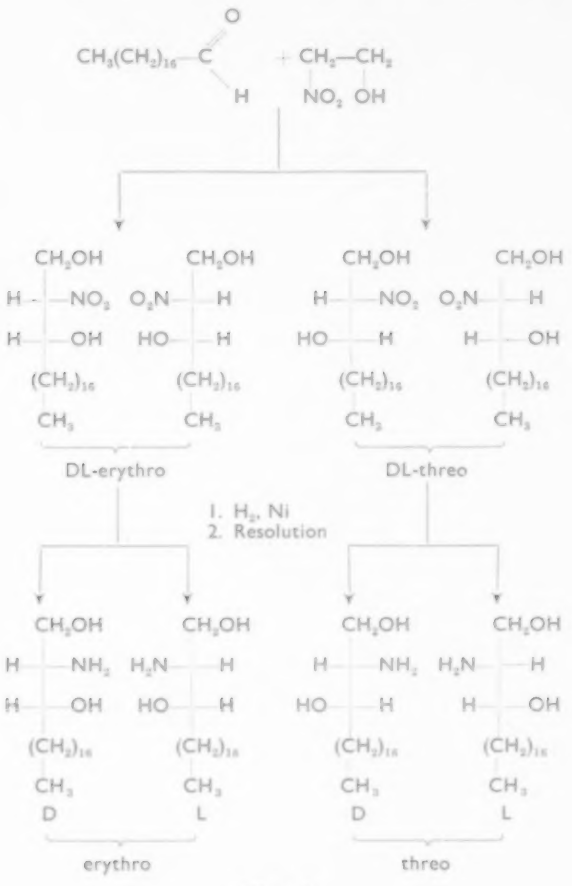


Chart 1.

the different solubility in a solvent mixture ether–pentane. The less soluble threo-isomer was obtained in an analytically pure condition. The yield of separated and purified nitrodiols was 56 per cent. The nitrodiols A (DL-threo-isomer) and B (DL-erythro-isomer) were hydrogenated separately in the presence of Raney nickel catalyst. Very good yields of pure threo-1,3-dihydroxy-2-aminoeicosane were obtained, while the erythro-aminodiol was purified less satisfactorily. However, the racemic aminodiols were best purified by converting them into the sparingly soluble oxalates. Treatment of the latter with potassium hydroxide followed by extraction with chloroform furnished the analytically pure bases.

The resolution into the optically active compounds of both racemic aminodiols thus prepared was effected by means of L-glutamic acid. This acid has repeatedly been applied as a very efficient resolving agent in the field of the sphingolipid bases.[6–9] One crystallization from 80 per cent ethanol of the less soluble glutamic acid salt was usually sufficient to attain the optically pure compound. The filtrates contained the more soluble glutamates. Their optical purity was satisfactory even when the filtrates were evaporated to dryness without further crystallizations.

TABLE I. COMPARISON OF MELTING POINTS AND SPECIFIC ROTATIONS OF OPTICALLY ACTIVE AND RACEMIC 1,3-DIHYDROXY-2-AMINOEICOSANES AND THEIR DERIVATIVES

Compound	M.p.	$[\alpha]_D$ in °
DL-Threo-base	99·5–100·5	
Oxalate	189–191	
DL-Erythro-base	81–83	
Oxalate	201–205	
+-Threo-base	108·5–109·5	+17·6
Glutamate I	153–156	
−-Threo-base	108–109	−17·7
Glutamate II	169–171	
+-Erythro-base	89–91	+9·7
Glutamate III	151–156	
−-Erythro-base	85–90	−9·9
Glutamate IV	155–167	

Furthermore, it was of interest to provide evidence as to the stereochemistry of synthetic C_{20}-dihydrosphingosines. In assigning threo and erythro structures to the synthetic C_{20}-bases following types of evidence were considered: chemical reactions, physical properties and infra-red spectra. The assignment of structure was based on the agreement in the relative behaviour of the C_{20}-isomers as compared to the C_{18}-isomers. Thus, from a consideration of melting points, infra-red spectra and analogy of chemical preparations, we conclude that the enantiomers melting at 108·5–109·5° and 108–109° showing $[\alpha]_D = +17{\cdot}6°$ and $-17{\cdot}7°$ respectively are the threo-forms, while the others melting at 89–91° and 85–90° showing $[\alpha]_D = +9{\cdot}7°$ and $-9{\cdot}9°$ are the erythro-forms. The melting points and specific rotations of the described compounds are summarized in Table 1.

In respect to the infra-red spectra there exist remarkable differences between the threo and erythro-isomers, which were observed consistently in both the C_{18} and C_{20}-series (Fig. 1). This observation offers a reliable means of assignment of erythro or threo structure.

Moreover, it is possible to assign the D-configuration to the +-erythro-C_{20}-dihydrosphingosine and, consequently, the L-configuration to the −-enantiomer. Namely, the stereochemistry of the C_{18}-bases has been completely elucidated by earlier workers. It has been well known that natural C_{18}-sphingosine and C_{18}-dihydrosphingosine possess the D+-erythro-configuration. The close agreement in physical properties of the +-erythro-C_{20}-base and natural dihydrosphingosine from horse brain—which represents a mixture of C_{18} and C_{20}-bases—is seen in Table 2 and Fig. 1.

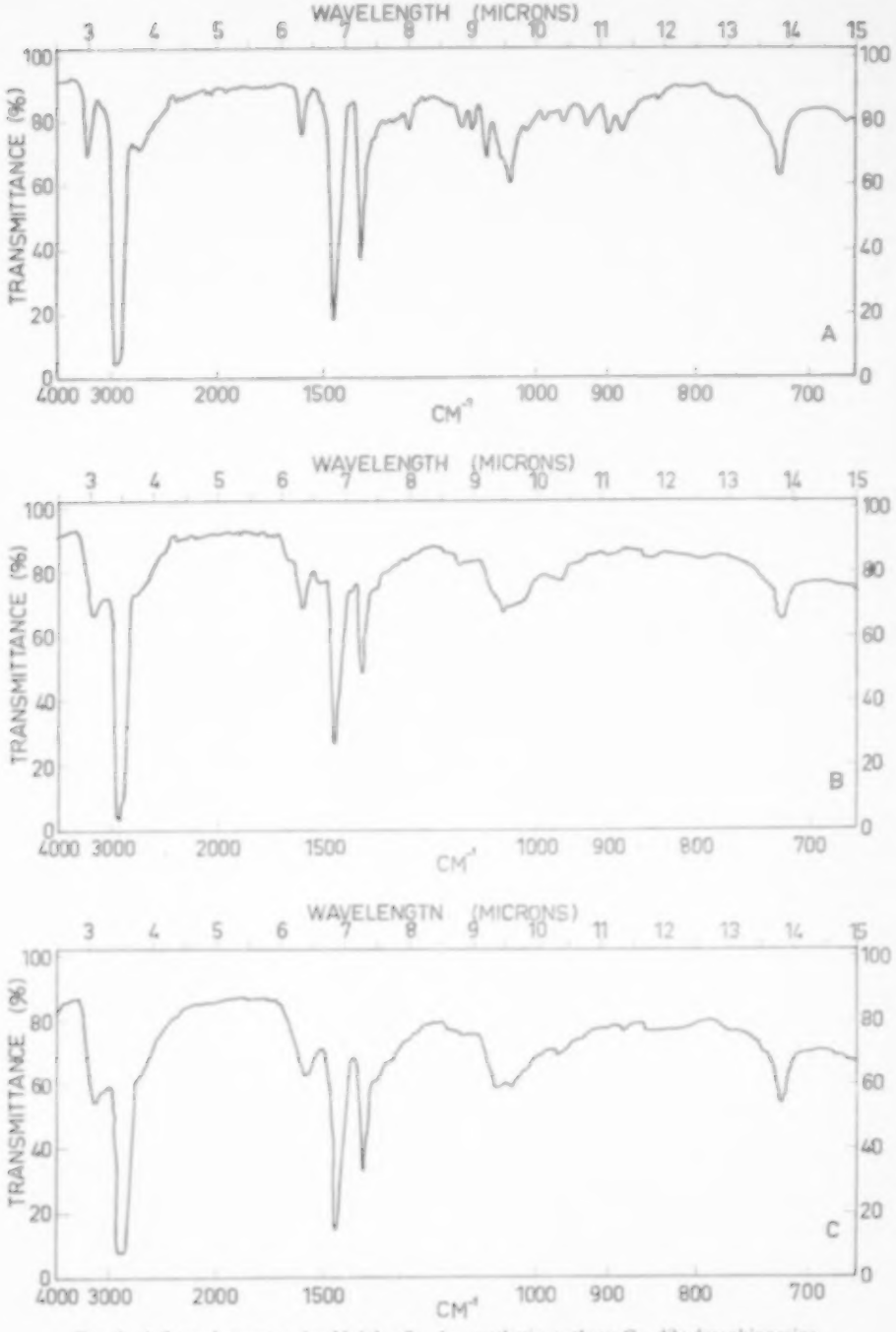


FIG. 1. Infra-red spectra in Nujol of: A—synthetic ±-threo-C_{20}-dihydrosphingosine, B—synthetic ±-erythro-C_{20}-dihydrosphingosine, C—natural ±-dihydrosphingosine (from horse brain).

EXPERIMENTAL

All melting points are uncorrected. Rotations were measured in chloroform. Microanalyses were carried out by Mrs. M. Munk-Weinert (Department of Chemistry, Medical Faculty, University of Zagreb). Infra-red absorption spectra were measured on a Perkin–Elmer Model 134 spectrophotometer by Mr. T. Magjer.

Octadecanal-1. The substance was obtained by the Rosenmund reduction of stearoyl chloride. The acid chloride was prepared in the usual manner by heating stearic acid and thionyl chloride at 70° for 1 hr and distillation of the reaction product; b.p. 195–202°/15 mm. Stearoyl chloride (18 g) was dissolved in dry xylene (80 ml), 5% palladium on barium sulphate catalyst (8 g) was added and reduced

TABLE 2. COMPARISON OF MELTING POINTS AND SPECIFIC ROTATIONS OF SYNTHETIC ±-ERYTHRO-C_{20}-DIHYDROSPHINGOSINE AND DIHYDROSPHINGOSINE FROM HORSE BRAIN

Compound	M.p.	$[\alpha]_D$ in °
±-Erythro-C_{20}-Base (synth.)	89–91	+9.7
Triacetyl	94–96	+17·3*
Dihydrosphingosine (natural)	90–92	+8·8
Triacetyl	91–94	+19·8*

* Carter and Shapiro[8] reported the following data: Natural triacetyl-C_{18}-dihydrosphingosine, m.p. 100–102°, $[\alpha]_D = +18°$ (in chloroform); synthetic triacetyl-C_{18}-dihydrosphingosine, m.p. 98–100°, $[\alpha]_D = +19·2°$ (in chloroform).

The mixed melting points of synthetic and natural base was 89–90°, and of triacetyl derivatives 93–95°.

in the hydrogen atm. After 1 hr 83% of the calculated amount of hydrogen chloride was evolved. Three such runs gave 31 g (66·5%) of the distilled aldehyde, b.p. 200–215°/20 mm. It solidified on standing at room temp.

DL-*Threo and* DL-*erythro*-1,3-*dihydroxy*-2-*nitroeicosane*. To a cooled solution of octadecanal-1 (16 g, 0·059 mole) in methanol (30 ml) nitroethanol (6 g, 0·066 mole) and potassium carbonate (1·4 g) were added. The mixture was shaken for 8 hr and then left to stand at room temp for 24 hr. The reaction mixture was then treated with water and acidified cautiously with methanolic hydrogen chloride. It was extracted with a large volume of ether, the combined ether extracts washed repeatedly with water and dried over sodium sulphate . Evaporation of the solvent yielded 18·7 g of a sticky residue which was dissolved in ether (30 ml). After addition of 300 ml of pentane and standing at room temp overnight, the resulting precipitate of the threo-isomer (nitrodiol A; 4·95 g, m.p. 54–68°; recrystallized from ether–pentane: m.p. 71–85°) was collected. The filtrate was concentrated to a smaller volume and cooled in the refrigerator. A second crop of crystals representing the erythro-isomer (nitrodiol B; 6·9 g, m.p. 46–50°; recrystallized from pentane: m.p. 53–57°) was obtained. The yield on both isomers was 11·85 g (56%). For analysis the threo-racemate was recrystallized three times from ether–pentane; colourless crystals, m.p. 87–88°. (Found: C, 67·15; H, 11·13; N, 3·97. $C_{20}H_{41}NO_4$ requires: C, 66·81; H, 11·49; N, 3·90%).

The erythro-racemate could not be purified sufficiently enough to give the correct elementary analysis. It melted at 63–67° and contained a small quantity of octadecanal.

DL-*Threo*-1,3-*dihydroxy*-2-*aminoeicosane*. The threo-nitrodiol A (2 g, m.p. 77–80°) was dissolved in 95% ethanol (30 ml) and hydrogenated in the presence of Raney nickel catalyst prepared from ca. 1 g of alloy. After 1 hr a theoretical amount (3 moles) of hydrogen was taken up at atmospheric press and room temp. The catalyst was removed by filtration and the filtrate evaporated to dryness to yield 1·8 g (97%) of the crude base, m.p. 67–73°. Recrystallization from 95% ethanol gave colourless crystals, m.p. 87–94°. Further purification could be effected by converting the base into the oxalate. The solution of the base (1·59 g) and oxalic acid (580 mg) in absolute ethanol (each in 5 ml) were mixed and cooled in the refrigerator for 5 hr. The precipitate was filtered off and washed twice

[6] C. A. Grob and E. F. Jenny, *Helv. Chim. Acta* **35**, 2106 (1952).
[7] D. E. Sunko and M. Prošťenik, *J. Org. Chem.* **18**, 1523 (1953).
[8] H. E. Carter and D. Shapiro, *J. Amer. Chem. Soc.* **75**, 5131 (1953).
[9] D. Shapiro, H. Segal and H. M. Flowers, *J. Amer. Chem. Soc.* **80**, 1194 (1958).

with boiling ethanol; crystalline solid (750 mg, 50%), m.p. 189–191°. After two crystallizations from glacial acetic acid the m.p. of the oxalate remained unchanged. (Found: C, 67·29; H, 11·87;. $C_{21}H_{41}NO_4$ requires: C, 67·33; H, 11·87%).

The pure threo-base was prepared by shaking the oxalate (1·3 g) with N KOH (25 ml) and chloroform (500 ml). After removal of the solvent 566 mg (49%), m.p. 97–98°, of the colourless solid was obtained. For analysis it was recrystallized three times from methanol; glistening meedles, m.p. 99·5–100·5°. (Found: C, 72·80; H, 12·89; $C_{20}H_{43}NO_2$ requires: C, 72·89; H, 13·15%).

DL-*Erythro*-1,3-*dihydroxy*-2-*aminoeicosane*. The erythro-nitrodiol B (1·98 g, m.p. 59–64°) was reduced in the same manner as described for the threo-isomer. The crude base (1·8 g) was converted into the oxalate which was purified only by washing with hot ethanol due to the insolubility in organic solvents. The yield of the colourless oxalate, m.p. 201–205°, amounted to 1·75 g (65%). (Found: C, 67·68; H, 11·49. $C_{21}H_{41}NO_4$ requires: C, 67·33; H, 11·84%).

The pure erythro-base was obtained from the oxalate (1·7 g) in the conventional way. Thereby, after three crystallizations from acetonitrile followed by two crystallizations from methanol, 840 mg of the analytically pure meedles, m.p. 81–83°, were obtained. (Found: C, 72·68; H, 12·89. $C_{20}H_{43}NO_2$ requires: C, 72·89; H, 13·15%).

Resolution of DL-*threo*-1,3-*dihydroxy*-2-*aminoeicosane*. L-Glutamic acid (950 mg) was dissolved in hot 50% ethanol (100 ml) and to this solution the racemic threo-base (2·1 g, m.p. 98–99°) in hot 95% ethanol (50 ml) was added. The turbid solution was left to stand at room temp for 3 hr. The crystalline precipitate was filtered off; yield 1·3 g, m.p. 146–149°. After concentration of the mother liquor a second crop of crystals (480 mg, m.p. 158–169°) was obtained. Total yield 1·78 g (59%). Recrystallization from 80% ethanol (400 ml) gave glistening leaflets, m.p. 153–156°: glutamate I. (Found: N, 5·92. $C_{25}H_{52}NO_8$ requires: N, 5·88%).

The mother liquor after the removal of the less soluble glutamate was concentrated, cooled in the refrigerator over-night and the crystalline precipitate separated by filtration. The diastereoisomeric glutamate was recrystallized three times from 80% ethanol (75 ml each); colourless needles, m.p. 168–171°: glutamate II. (Found: N, 6·14; $C_{25}H_{52}NO_6$ requires: N, 5·88%).

+-*Threo*-1,3-*dihydroxy*-2-*aminoeicosane*. The glutamate I with m.p. 153–156° (1·1 g) was decomposed with 2 N Na_2CO_3 (30 ml) and the base was extracted with much chloroform. The combined extracts were washed with water, and evaporated to dryness to yield 529 mg (69%) of the crude base melting at 107–108°. Three crystallizations from chloroform gave glistening needles, m.p. 108·5–109·5°, $[\alpha]_D^{26} = +17·6° \pm 1°$ (*c*, 0·5). (Found: C, 73·01; H, 13·11. $C_{20}H_{43}NO_2$ requires: C, 72·89; H, 13·15%).

−-*Threo*-1,3-*dihydroxy*-2-*aminoeicosane*. The glutamate II with m.p. 169–171° (450 mg) was decomposed in the same manner as described above yielding 303 mg of the crude base. Crystallization from chloroform gave glistening needles, m.p. 108–109°, $[\alpha]_D^{27} = -17·7° \pm 1°$ (*c*, 0·372). (Found: C, 72·79; H, 13·00. $C_{20}H_{43}NO_2$ requires: C, 72·89; H, 13·15%).

Equal amounts (3 mg) of both enantiomeric threo-bases were mixed and the mixture was crystallized from methanol. The product melted at 99–100° and showed no depression with the starting racemic base.

Resolution of DL-*erythro*-1,3-*dihydroxy*-2-*aminoeicosane*. The DL-erythro-base (840 mg) was resolved with L-glutamic acid (425 mg) in the same manner as described for the threo-racemate. The first crop of crystals (442 mg) melted at 89–110° and was a mixture of the unreacted base and glutamic acid. The second crop of crystals (562 mg) melted at 150–163°. After three crystallizations from 80% ethanol the m.p. was 151–156°: glutamate III. (Found: N, 5·20. $C_{25}H_{52}NO_6$ requires: N, 5·88%).

The mother liquor after the separation of the less soluble glutamate III was evaporated to dryness and the residue (340 mg) recrystallized three times from 80% ethanol; colourless powder, m.p. 155–167°: glutamate IV. (Found: N, 6·03. $C_{25}H_{52}NO_8$ requires: N, 5·88%).

+-*Erythro*-1,3-*dihydroxy*-2-*aminoeicosane*. The base recovered from the glutamate III (m.p. 151–156°) was crystallized from methanol and then from acetonitrile; m.p. 89–91°, $[\alpha]_D^{27} = +9·7° \pm 2°$ (*c*, 0·46).

Triacetyl-derivative. The +-erythro-base (97 mg), acetic anhydride (1 ml) and pyridine (1 ml) were mixed and allowed to stand at room temp for 24 hr. The reaction mixture was evaporated to dryness, dissolved in ether, washed successively with N HCl and water and the solvent removed by distillation. The crude product (38 mg, m.p. 71–74°) was recrystallized three times from acetone; m.p. 94–96°, $[\alpha]_D^{22} = +17·3° \pm 1°$ (*c*, 0·29).

—-*Erythro*-1,3-*dihydroxy*-2-*aminoeicosane*. The base obtained from the glutamate IV (m.p. 155–167°) was recrystallized from acetonitrile; colourless powder, m.p. 85–90°, $[\alpha]_D^{22} = -9{\cdot}9° \pm 2°$ (*c*, 0·534).

Equal amounts of both enantiomeric erythro-bases were mixed and the mixture was crystallized from methanol. The product melted at 70–73° and showed no depression with the starting racemic base.

Dihydrosphingosine. Crude sphingosine sulphate isolated from horse brain was treated with N NaOH and the free base extracted with ether. After crystallization from acetonitrile it melted at 90–92°; $[\alpha]_D^{22} = +8{\cdot}8° \pm 2°$ (*c*, 0·57).

Triacetyl-derivative. Prepared as described above and recrystallized from acetone it melted at 91–94°; $[\alpha]_D^{22} = +19{\cdot}8° \pm 1°$ (*c*, 0·83).

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KETOVINYLATION OF β-DICARBONYL COMPOUNDS*

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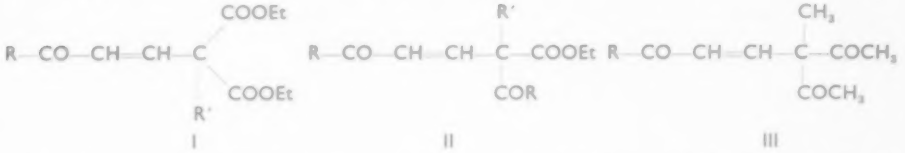
(*Received* 13 *July* 1960)

Abstract—The introduction of the ketovinyl group into β-dicarbonyl compounds with only one labile hydrogen proceeds normally, but the presence of two labile hydrogens results in the formation of complex mixtures. Ethyl malonate and ethyl acetoacetate have, however, been successfully ketovinylated. In the former case, α-carbethoxy-δ-keto-β,γ-unsaturated acids are produced in high yield and depending on the conditions of ketovinylation of ethyl acetoacetate either 4-alkyl salicyclic acids or polysubstituted benzene derivatives may be prepared. Further, the ketovinylation products of ethyl malonate and alkyl acetoacetates may be used for the synthesis of either (1) unsaturated aliphatic keto acids or diketones or (2) a variety of α-pyrone derivatives. A mechanism for the ketovinylation of ethyl acetoacetate is proposed and the *trans* configuration of the ketovinylation products established.

β-CHLORVINYLKETONES, RCOCH=CHCl, are easily prepared and highly reactive,[1] the labile halogen atom being readily substituted by different groups (I, SCN, NR_2, OAr, OAlk, SR, etc.) The reaction of β-chlorvinylketones with β-dicarbonyl compounds possessing labile hydrogen atoms, yields polyfunctional compounds with a highly reactive ketovinyl group. This ketovinylation, or the introduction of the ketovinyl group into β-dicarbonyl compounds, is a new example of substitution of the methylene group and may be considered intermediate between alkylation and acylation, the β-chlorvinyl ketones, as far as lability of the halogen is concerned, occupying a position intermediate between the alkyl and acyl halides.

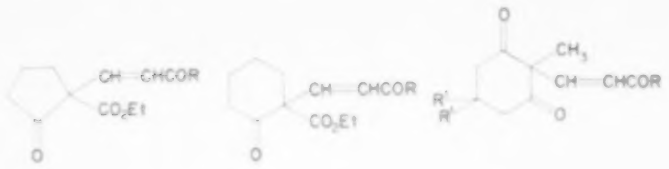
Ketovinylation of β-dicarbonyl compounds with only one labile hydrogen proceeds normally. Various alkylmalonates,[2] α-alkylacetoacetates[3] and α-alkyl benzoyl-



acetates[4] react to yield δ-keto-α-carbethoxy- and δ-keto-α-acyl-derivatives of β,γ-unsaturated acids I and II. β-Diketones[5] with a single labile hydrogen such as 3-methyl-2,4-pentadione form unsaturated triketones III. Ketovinylation of cyclic β-keto acids[6] and β-diketones[5] also proceed as expected, 2-carbethoxycyclopentanone, 2-carbethoxycyclohexanone and 2-methylcyclohexanedione or dimedone yielding compounds of the type IV, V and VI respectively. Ketovinylation of diacetylacetate (α-acetylacetoacetate) has failed.

* Translated by A. L. Pumpiansky, Moscow.

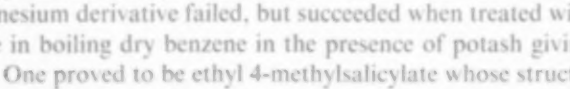
[1] N. K. Kochetkov, *Uspechi chimii* **24**, 32 (1955).
[2] N. K. Kochetkov and L. I. Kudrjashov, *J. Gen. Chem. U.S.S.R.* **26**, 851 (1956).
[3] N. K. Kochetkov, B. P. Gottich and L. I. Kudrjashov, *J. Gen. Chem. U.S.S.R.* **28**, 1508 (1958).
[4] W. F. Beljaev, M. N. Belokurskaja and N. K. Kochetkov, *J. Gen. Chem. U.S.S.R.* **30**, 1492 (1960).
[5] N. K. Kochetkov, and B. P. Gottich, *J. Gen. Chem. U.S.S.R.* **30**, 948 (1960).
[6] N. K. Kochetkov, B. P. Gottich and R. Stumpf, *J. Gen. Chem. U.S.S.R.* **29**, 1320 (1959).



IV V VI

The yields of products obtained by ketovinylation of β-dicarbonyl compounds with one labile hydrogen depend on the nature of the β-dicarbonyl compound, the α-substituted acetoacetates and alkylmalonates resulting in higher yields than the β-diketones. Table 1 shows that the yield of ketovinylation decreases with increasing enolization. The reason for this correlation is not clear and is being investigated.

In contrast ketovinylation of β-dicarbonyl compounds with two α-hydrogen atoms is involved (see below) and in the case of ethyl acetoacetate and malonate leads to complex mixtures thus invalidating the method. It has, however, proved possible to ketovinylate ethyl malonate by reacting the ethoxymagnesium derivative with β-chlorovinylketones in benzene. This proceeds smoothly to give esters of α-carbethoxy-δ-keto-β,γ-unsaturated acids in high yield.[7] The compounds obtained readily form α-pyrone derivatives (see below). With ferric chloride they turn cherry-red indicating a keto-enol tautomerism.



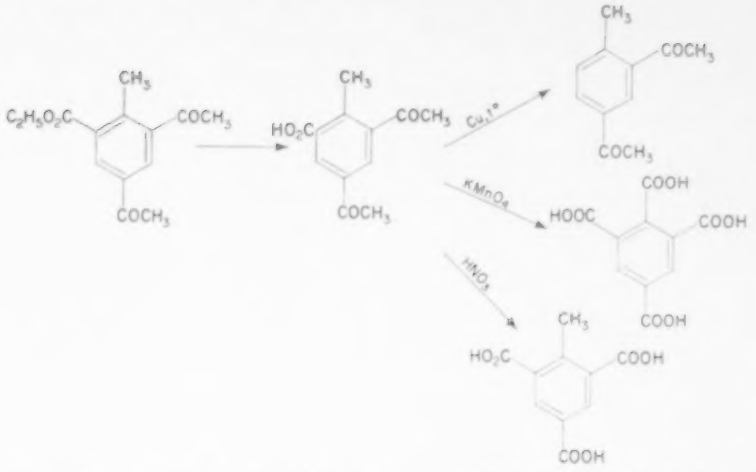
Ketovinylation of ethyl acetoacetate under similar conditions, that is, with ethoxymagnesium derivative failed, but succeeded when treated with methyl-β-chlorovinylketone in boiling dry benzene in the presence of potash giving rise to two compounds.[8,9] One proved to be ethyl 4-methylsalicylate whose structure was established by conversion to methoxyterephthalic acid. The second compound was shown by the following reactions to be 2-methyl-3,5-diacetylbenzoate.

The homologs of methyl-β-chlorovinylketone react similarly with ethyl acetoacetate in the presence of potash following the same scheme to form the two types of compounds.[8,9]

TABLE 1. ENOLIZATION OF β-DICARBONYL COMPOUNDS AND YIELDS OF KETOVINYLATED PRODUCTS

β-Dicarbonyl compound	Enolization (%)		Yields of ketovinylated products
	in abs. alc.	in benzene	
α-Ethyl-acetoacetate	2·8	4·2	55–66
α-n-Butyl-acetoacetate	2·4	6·2	55–66
Carbethoxycyclopentanone	5·9	8·2	64–87
Methylacetylacetone	39·8		44–59
Carbethoxycyclohexanone	61·7	74·8	61–65
Methyldihydroresorcine	93·8		25–26
α-Acetylacetoacetate	96–100		0

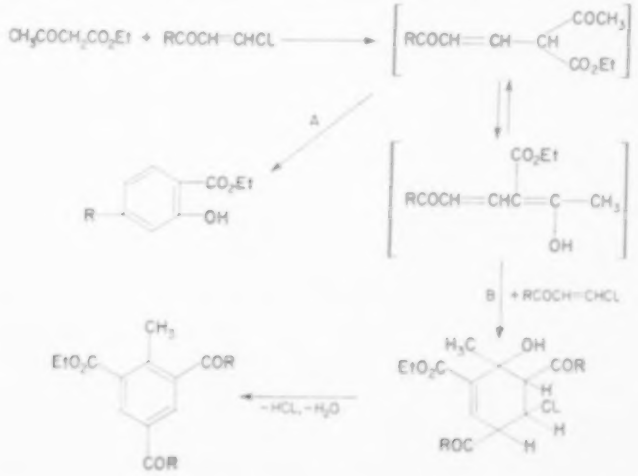
[7] N. K. Kochetkov and L. I. Kudrjashov, *J. Gen. Chem. USSR* **27**, 243 (1957).
[8] N. K. Kochetkov, L. I. Kudrjashov and A. N. Nesmejanov, *Izv. Akad. Nauk. SSSR* 809 (1955).
[9] N. K. Kochetkov, L. I. Kudrjashov and T. M. Senchenkowa, *J. Gen. Chem. USSR* **29**, 650 (1959).



The ratio of the two compounds formed depends on the ratio of ethyl acetoacetate to β-chlorovinyl ketone. Thus, condensation of methyl-β-chlorovinylketone with excess acetoacetate leads to higher yields of 4-methylsalicylate, a tenfold excess yielding 30–40 per cent together with about 20 per cent of 2-methyl-3,5-diacetylbenzoate. On the other hand, decreasing amounts of acetoacetate gives rise to increased yields of 2-methyl-3,5-diacylbenzoate and with ethyl acetoacetate and β-chlorovinylketone in the ratio of 1:1·5 it is the only product being produced in about 80 per cent yield. These alternative routes are of interest in that they facilitate the preparation of 4-alkylsalicylic acids and polysubstituted benzene derivatives.

The formation of these two products may be accounted for as follows: The first condensation product, the ketovinylation of ethyl acetoacetate in the presence of potash, undergoes one of two conversions—either to salicylic acids or polysubstituted benzene derivatives.

Cyclization (route A) following the crotonic acid type condensation proceeds, as it should, with a more active methyl of the acetyl group of the acetoacetate to give



salicylic acid derivatives. In the second type of conversion (route B), undergoes enolization and condenses as a diene with a second molecule of β-chlorovinylketone, this reaction being possible.[1] The unstable adduct so formed loses water and hydrogen chloride and undergoes aromatization to a polysubstituted benzene derivative. In this connexion, the behaviour of the enolic form of γ-ketoalkenylacetoacetate as a diene in the diene synthesis is of interest. Such a type of diene being hitherto unknown and this reaction being a new diene synthesis. While this work was in progress, Braude[10] published the dimerization of mesityl oxide by the action of lithium and postulated the diene condensation with mesityl oxide enolate. Thus, the ketovinylation of compounds involving more than one labile hydrogen is complicated by fast conversion processes of starting products of mono-ketovinylation. The third route consists in the ready cyclization of the above products to α-pyrone derivatives, as shown below.

The configuration of ketovinylation products

There is no information in the literature on the configuration of β-chlorovinylketones although their synthesis by condensation of acyl chlorides with acetylene in the presence of aluminium chloride,[1] suggests the more stable *trans*-configuration. This has been proved experimentally.[11]

Oxidation of β-methylchlorovinylketone with sodium hypochlorite at room temperature under carefully controlled conditions results in *trans*-β-chloroacrylic acid as the only product. Therefore, methyl-β-chlorovinylketone as well as all its homologs obtained under similar conditions must be *trans*.

The configuration of ketovinylation products of β-dicarbonyl compounds was determined by investigation of infra-red spectra,[12] purely chemical methods being impossible due to ease of isomerization at the double bond. Infra-red spectra of α-ethyl-α-(3-ketobutenyl)-acetoacetate (II, $R = R' = CH_3$, $R'' = C_2H_5$) and (3-ketobutenyl)-methylacetylacetone (III, $R = CH_3$) revealed an intensive band at 986–984 cm^{-1} due to non-planar deformation vibrations of hydrogen atoms and appearing only with *trans*-configuration at the double bond. This indicates that the ketovinylation products (I, II and III) must be *trans* and, hence, the ketovinylation reaction proceeds without change of configuration.

As these compounds were isolated by distillation at high temperatures, isomerization of the primarily reaction products during isolation and purification could not be avoided.

In order to remove all doubt the configuration of phenyl-1-3-ketobutenylsulphone (VII), produced by the reaction of methyl-β-chlorovinylketone and sodium phenylsulphinate[13] under conditions that preclude isomerization during ketovinylation, was determined,

$$CH_3COCH{=}CHSO_2C_6H_5.$$
VII

Infra-red spectra of VII and its dinitrophenylhydrazone reveal an intensive band in the 983 cm^{-1} range, thus indicating a *trans*-configuration. The crystalline sulphone

[10] E. Braude, B. Jofton, L. Lowe and E. Waight, *J. Chem. Soc.* 4054 (1956).
[11] N. K. Kochetkov, B. P. Gottich, M. Ia. Karpeisky and R. M. Chomutov, *Chem. Nauka i prom.* **3**, 834 (1958).
[12] N. K. Kochetkov, B. P. Gottich, W. G. Winokurov and R. M. Chomutov *Dokl. Akad. Nauk SSSR* **125**, 89 (1959).
[13] N. K. Kochetkov and W. N. Winogradowa, *J. Gen. Chem. U.S.S.R.* **27**, 2745 (1957).

VII when exposed for over 100 hours to ultra-violet irradiation becomes liquid. The infra-red spectra of the liquid sulphone (not distilled to avoid any possible isomerization) and its dinitrophenylhydrazone show no absorption bands in the 990–965 cm^{-1} range, indicating a *cis*-configuration. Therefore, the crystalline sulphone is *trans* and the 983–986 cm^{-1} band is characteristic of the *trans*-double bond in the systems under investigation.

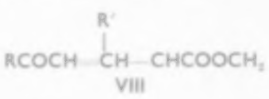
Ketovinylation products have therefore, a *trans*-configuration and the starting β-chlorovinylketones retain their configuration during the reaction. This can be accounted for in terms of the substitution mechanism of the halogen atom in β-chlorovinylketones previously suggested by one of the authors.[1]

VOL. 12 1961

Synthesis of unsaturated aliphatic keto-acids and diketones

Esters of δ-keto-α-carbethoxy-β,γ- unsaturated acids (I) and those of δ-keto-α-acyl-β,γ-unsaturated acid (II) produced by ketovinylating alkylmalonates and alkylacetoacetates can be used as starting compounds for the syntheses of unsaturated aliphatic keto acids.

Compounds of the type I on treatment with basic agents undergo a characteristic conversion, one of the carbethoxy groups splitting off, and producing esters of δ-keto-β,γ-unsaturated acids VIII, vinylogs of α-alkylacetoacetates.[14]

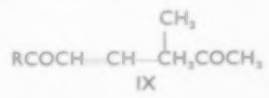


VIII

This conversion is similar to that of acylmalonates,[15] this reaction being a new example of vinylogy. It takes places under the action of potassium hydroxide in methanol and is accompanied by *trans*-esterification of the ester grouping. The use of ethanol leads to poorer results. It is more convenient to obtain esters of δ-keto-β,γ-unsaturated acids VIII from esters of δ-keto-α-acyl-β,γ-unsaturated acids II, by treatment with bases.[16]

Compounds of type II being labile, strong bases (alcoholates and alkali) fail owing to complicated cyclization processes, but with aqueous ammonia and ammonium chloride the reaction produces a high yield of VIII.

There is an optimum ammonia concentration for the conversion of each particular compound, as an increase in molecular weight hinders the formation of VIII. A similar conversion is also observed for triketones[5] of type III. Treatment with aqueous sodium hydroxide at room temperature gives rise to smooth cleavage of acyl groups yielding a high percentage of unsaturated diketones,[5] vinylogs of β-diketones.



IX

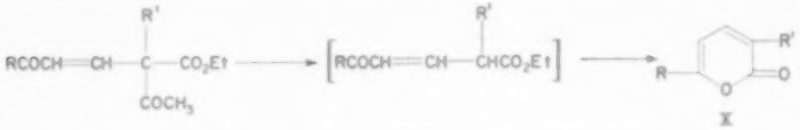
An attempt to degrade the ketovinylation product of ethyl malonate (I, R′ = H) to obtain vinylogs of esters of unsubstituted β-ketoacids failed, but these compounds have been obtained in an indirect way (see below).

[14] N. K. Kochetkov, L. I. Kudrjashov and R. A. Aleewa, *J. Gen. Chem. U.S.S.R.* **27**, 2166 (1957).
[15] M. Conrad, C. Bischoff and M. Gutzeit, *Liebigs Ann.* **214**, 31 (1882).
[16] N. K. Kochetkov and B. P. Gottich, *J. Gen. Chem. U.S.S.R.* **28**, 2732 (1958).

Synthesis of α-pyrone derivatives

The action of acidic reagents on the ketovinylation products of types I, II, IV, and V has been investigated and in each case cyclization to α-pyrone derivatives takes place.

Heating esters of δ-keto-α-acyl-β,γ-unsaturated acids (II) with mineral acids, (best of all with a mixture of hydrochloric and acetic acid) gives rise to 3,6-disubstituted α-pyrones (X) in a high yield.[17] It has been shown[17] that the reaction proceeds through

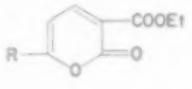


X

a preliminary acidic degradation of II, which is then cyclized in acidic medium to pyrone derivatives.

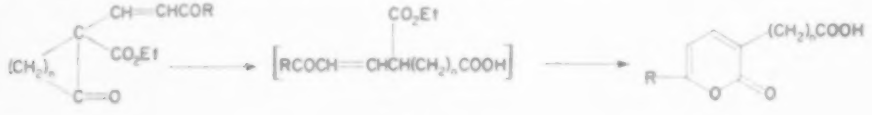
In all cases of acidic degradation investigated no ketonic scission could be effected.

The pyrone derivatives are most readily produced from ketovinylation products of ethyl malonate, that is from esters of δ-keto-α-carbethoxy-β,γ- unsaturated acids (I). The latter are cyclized to esters of 6-substituted pyronecarboxylic acids (XI) under the action of various acidic agents as well as at elevated temperatures.[7] These reactions present difficulties when isolating I in a pure state as on distillation α-pyrone derivatives are readily produced. Compound XI is best produced by heating I with acetic anhydride and acetyl chloride, it not being necessary to purify I first.[18]



XI

The ketovinylation products of cyclic β-ketoacids IV and V when treated with a mixture of hydrochloric and acetic acids also give rise to α-pyrone derivatives. This is accompanied by the simultaneous opening of the alicyclic ring to give previously unavailable (6-alkyl-α-pyronoyl-3)-alkancarboxylic acids XII.[17]



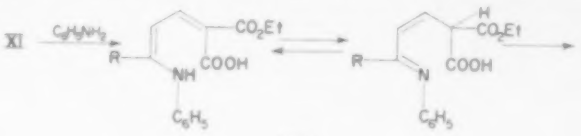
n = 3,4 XII

Ketovinylation products of dicarbonyl compounds are therefore useful starting products for the synthesis of a variety of pyrone derivatives.

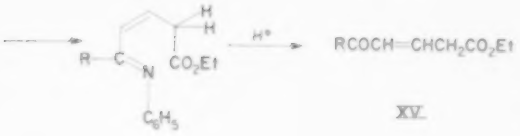
In conclusion, starting with α-pyrone derivatives, namely with 6-alkyl-3-carbethoxy-α-pyrones, we succeeded in obtaining formerly unknown vinylogs of β-keto-acids. This synthesis is possible due to our new method of opening the α-pyrone ring.[19] It has been shown that the reaction of 6-methyl-3-carbethoxy-α-pyrone XI and aniline leads to the opening of the ring to form α-carbethoxy-δ-N-phenylaminosorbic acid

[17] N. K. Kochetkov and B. P. Gottich, *J. Gen. Chem. U.S.S.R.* **29**, 1324 (1959).
[18] N. K. Kochetkov and L. I. Kudrjashov, *J. Gen. Chem. U.S.S.R.* **28**, 1511 (1958).
[19] N. K. Kochetkov and L. I. Kudrjashov, *J. Gen. Chem. U.S.S.R.* **28**, 3020 (1958).

(XII, R = CH_3) which, on careful heating decarboxylates to δ-N-phenylaminosorbic acid (XIV, R = CH_3). The latter on treatment with dilute acids, splits off aniline giving ethyl-5-keto-hexene-3-oate (XV, R = CH_3), a vinylog of ethyl acetoacetate.



XIII



XIV XV

Similarly, other 6-alkyl-3-carbethoxy-α-pyrones give rise to vinylogs of esters of β-ketoacids (XV R = C_3H_7, n—C_5H_{11}).

EXPERIMENTAL

Ketovinylation of esters of alkylmalonic acid. To a suspension of sodium ethyl alkylmalonate (0·2 mole) in benzene (200 cc) cooled with ice, a solution of β-chlorovinylketone (0·2 mole) in dry benzene (100 cc) was gradually added (1 hr) with stirring and the reaction mixture then refluxed for 2–2½ hr. After treatment with water and further extraction with benzene, the solvent was removed and the residue distilled *in vacuo*. The constants, yields, and analyses of the alkyl-(3-ketoalkenyl) malonates produced are listed in Table 2. Ketovinylation of α-alkylacetoacetates, cyclic β-ketoacids, and methylacetoacetone was achieved under similar conditions and the constants, yields, and analyses of the products obtained are listed in Tables 3, 4, 5.

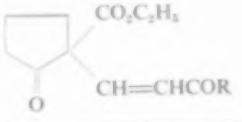
Ketovinylation of methyldihydroresorcine and methyldimedone. In contrast, the sodium derivatives of cyclic β-diketones were prepared in absolute methanol, the alcohol substituted by dioxan and twice

TABLE 2. $RCOCH{=}CHC(R')(CO_2Et)_2$

N°	R	R′	Yield (%)	b.p.	d_4^{20}	n_D^{20}	% C		% H	
							Found	Calc.	Found	Calc.
1	CH_3	C_2H_5	56	125–126°/2 mm	1·0598	1·4543	61·33 61·41	60·91	7·95 8·08	7·87
2	CH_3	C_3H_7	56	163°/8 mm	1·0437	1·4553	62·36 62·42	62·19	8·27 8·36	8·20
3	CH_3	C_4H_9	35	154–157°/4 mm	1·0326	1·4559	63·10 63·07	63·35	8·59 8·58	8·51
4	C_2H_5	C_3H_7	94	169–171°/9 mm	1·0350	1·4575	63·27 63·35	63·35	8·64 8·62	8·51
5	C_7H_{15}	C_3H_7	70	177–178°/1 mm	0·9901	1·4581	68·12 67·92	67·76	9·66 9·53	9·66
6	C_6H_5	C_3H_7	64	204–205°/4 mm	m.p. 39°		68·84 68·84	68·66	7·51 7·41	7·28

TABLE 3. $CH_3COCRCO_2C_2H_5$ / $CH{=}CHCOR'$

R	R'	b.p.	d_4^{20}	n_D^{20}	Yield	Analyses	
						Found	Calc.
C_2H_5	CH_3	108–110°/1 mm	1·0550	1·4670	64·5%	C 63·71 H 8·02	C, 63·91, 63·84 H, 8·07, 8·12
C_2H_5	C_2H_5	115–117°/1 mm	1·0415	1·4665	56·5%	C 64·97 H, 8·39	C, 65·32, 65·20 H 7·99, 8·05
C_2H_5	C_3H_7	120–122°/1 mm	1·0270	1·4657	64%	C, 66·11 H, 8·72	C, 66·02, 65·89 H, 8·53, 8·56
n—C_4H_9	CH_3	125–126°/1 mm	1·0274	1·4662	55%	C 66·11 H, 8·72	C, 65·98, 66·13 H, 8·77, 8·90
n—C_4H_9	C_2H_5	129–131°/2 mm	1·0157	1·4660	54%	C, 67·13 H, 9·01	C, 66·97, 67·01 H, 9·39, 9·42
n—C_4H_9	C_3H_7	137–138°/1 mm	1·0007	1·4650	66%	C, 68·06 H, 9·28	C, 68·30, 68·56 H, 9·48, 9·40

TABLE 4. 

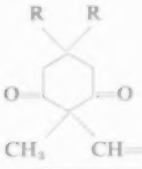
R	b.p.	m.p.	d_4^{20}	n_D^{20}	Yield	Analysis	
						Found	Calc.
CH_3	147–149/3 mm	—	1·1112	1·4880	65%	C, 64·28 H, 7·19	C, 64·41, 64·68 H, 7·35, 7·52
C_2H_5	153–155/3 mm	—	1·0958	1·4862	64%	C, 65·53 H, 7·62	C, 65·72, 65·86 H, 7·81, 7·87
C_3H_7	149–152/2 mm	—	1·0767	1·4840	67%	C, 66·63 H, 7·98	C, 66·54, 66·61 H, 7·98, 8·18
C_6H_5	154–156/0·03 mm	60–65°	—	—	49%	C, 71·33 H, 6·68	C, 71·60, 71·71 H, 6·48, 6·54
CH_3	163–164/4 mm	28·5–29°	—	—	64%	C, 65·56 H, 7·61	C, 65·72, 65·67 H, 7·40, 7·48
C_3H_7	168–169/2 mm	—	1·0722	1·4868	61%	C, 67·72 H, 8·33	C, 67·90, 67·82 H, 8·51, 8·52
C_6H_5	—	72–73°	—	—	65%	C, 71·98 H, 6·71	C, 71·89, 71·99 H, 6·94, 6·89

the required amount of methyl-β-chlorovinylketone used. After refluxing and cooling for 4 hr, the precipitate was filtered off, the solvent removed and the residue distilled *in vacuo*. The oils gradually crystallized and were recrystallized from dry ether. Constants, yields, and analyses of compounds obtained are listed in Table 6.

Ketovinylation of ethyl malonate. To magnesium (4·8 g), activated with iodine, a mixture of absolute alcohol (25 cc) and ethyl malonate (33·6 g), were added (heating if necessary to start the reaction) and gradually more alcohol (100 cc) was added with heating until a solution was obtained. Alcohol was then removed *in vacuo* and the residue dissolved in toluene (100 g). To the ethoxymagnesium malonate cooled to −10°, β-chlorovinylketone (0·15 mole) was added with stirring and left overnight. Cold water (100 cc) and conc hydrochloric acid (25 cc) were added, the organic layer isolated and the

TABLE 5. $CH_3CO(CH_3)CCOCH_3$ / $CH{=}CHCOR$

R	b.p.	d_4^{20}	n_D^{20}	Yield	Analyses	
					Found	Calc.
CH_3	100–101°/1 mm	1·0609	1·4860	59%	C, 65·91 H, 7·80	C, 66·27, 66·12 H, 7·78, 7·79
C_2H_5	106–107·5°/1 mm	1·0400	1·4822	44%	C, 67·32 H, 8·22	C, 67·56, 67·34 H, 8·24, 8·14
C_3H_7	116–118°/1 mm	1·0215	1·4795	59%	C, 68·55 H, 8·63	C, 68·86, 68·82 H, 8·82, 8·76

TABLE 6. 

R	b.p.	m.p.	Yield	Analyses	
				Found	Calc.
H	147–154°/4 mm	61–63·5°	26%	C, 68·02 H, 7·26	C, 68·26, 68·53 H, 7·43, 7·44
CH_3	147–149°/2 mm	37–38°	35%	C, 70·24 H, 8·16	C, 70·54, 70·65 H, 8·35, 8·25

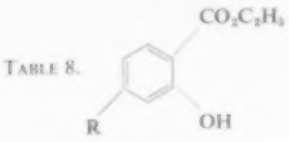
TABLE 7. $R{-}CO{-}CH{=}CH{-}CH(CO_2C_2H_5)_2$

No.	R	Yield	b.p.	d_4^{20}	n_D^{20}	MRD		% C		% H	
						Found	Calc.	Found	Calc.	Found	Calc.
1	CH_3	69·6	121–122/3 mm	1·1086	1·4646	56·88	55·85	57·66 57·70	57·88	7·04 7·04	7·07
2	C_2H_5	44	130–134/2 mm	1·0857	1·4611	61·25	60·48	59·17 59·30	59·49	7·67 7·69	7·49
3	C_3H_7	67	90–93/0·06 mm	1·061	1·4581	65·47	65·09	60·77 60·55	60·92	7·96 7·82	7·87

water layer extracted with toluene. After removing the solvent, the residue was distilled *in vacuo* in the presence of hydroquinone. Constants, yields, and analyses of the substance obtained are listed in Table 7.

Ethyl 4-alkylsalicylate. To a boiling mixture of ethyl acetoacetate (260 g), ground potash (30 g), and absolute toluene or xylol (100 cc), a solution of β-chlorovinylketone (0·2 mole) in 100 cc of solvent was added dropwise during 8 hr, heating continued for 1 hr, cooled, the residue filtered, washed with benzene, the filtrates evaporated and ethyl 4-alkylsalicylate isolated by distillation. The yield and constants of compounds obtained are listed in Table 8.

TABLE 8.



N°	R	Yield	b.p.	d_4^{20}	n_D^{20}
1	CH_3	39·2	129–132/11 mm	1·0915	1·5174
2	C_2H_5	18	141–142/15 mm	1·0784	1·5162
3	n-C_4H_9	17	138–140/6 mm	1·0836	1·5165
4	n-C_4H_9	18	148·5–150/9 mm	1·0878	1·5118

Ethyl 2-methyl-3,5-diacetylbenzoate. To a mixture of ethyl acetoacetate (260 g), finely ground anhydrous potash (2·76 g) and absolute benzene (180 cc), methyl-β-chlorovinylketone (133 g; 1·3 moles) was added during 1 hr with stirring. After refluxing for 4 hr, water (250 cc) was added, the benzene layer separated, the water layer extracted with ether, the combined extracts evaporated and ethyl 2-methyl-3,5-diacetyl benzoate distilled *in vacuo*, b.p. 160–165°/1 mm, yield 120·5 g (81%). After seeding, the compound crystallized, m.p. 61° and was recrystallized first from petroleum-ether benzene and then from aqueous methanol. (Found: C, 68·05, 67·97; H, 6·57, 6·52. $C_{14}H_{16}O_4$ requires: C, 67·76; H, 6·49%).

Ethyl 2-methyl-3,5-dibenzoylbenzoate was similarly obtained in 85·5% yield, m.p. 104° from aqueous alcohol. (Found: C, 77·79, 77·58; H, 5·51, 5·52. $C_{24}H_{20}O_4$ requires: C, 77·40; H, 5·41%).

Oxidation of methyl-β-chlorovinylketone with sodium hypochlorite. To an aqueous solution (820 cc) containing about 80 g sodium hypochlorite, methyl-β-chlorovinyl-ketone solution (15·6 g) in dioxan (50 cc) was added during 15–20 min keeping the temp at 29–30°. The mixture then stirred for 3½–4 hr at room temp, and the excess sodium hypochlorite eliminated. The solution obtained was reduced *in vacuo* (the water-bath temp not exceeding 40°) to 150–200 cc, acidified with 50% sulphuric acid and repeatedly extracted with ether; dried with $MgSO_4$ and the solvent removed. The solid dissolved in absolute alcohol (75 cc) was neutralized with potassium hydroxyde to pH 7–7·5. After 2 days only a trace of inorganic matter was precipitated from the alcoholic solution (0·04 g) indicating the absence of *cis*-β-chloroacrylic acid as the oxidation product (potassium salt of *cis*-β-chloroacrylic acid is insoluble in absolute ethyl alcohol). After acidifying and removing the solvent, *trans*-β-chloroacrylic acid was isolated from the alcoholic solution (7·8–8·0 g, 50%). After the second recrystallization from dil hydrochloric acid the m.p. of the compound was 84·86°. Lit. m.p. 85·5–86°[20] (Found: Cl, 33·44, 33·25. $C_3H_3O_2Cl$ requires: Cl, 33·28%).

Phenyl-(3-ketobutenyl)-sulphone and its conversions under the action of ultra-violet light. Phenyl-(3-ketobutenyl)-sulphone was prepared according to Kochetkov and Vinogradova[12] in 84% yield, m.p. 61–62°. The 2,4-dinitrophenylhydrazone was obtained from 96% ethyl alcohol in the presence of conc sulphuric acid as orange needles, m.p. 215–216° and crystallized from ethyl acetate. (Found: N, 14·56, 14·43. $C_{16}H_{14}N_4O_6S$ requires; N, 14·35%). (Infra-red spectra, see Fig. 1.) Two 1 g samples of phenyl (3-ketobutenyl) sulphone were each added to cryoscopic benzene (7 cc) in quartz ampoules and exposed to ultra-violet light for 50 hr, (see Fig. 2). One tube was then broken and the benzene removed *in vacuo*. From the residue, a colourless oil, (infra-red spectra of the sample are given in Fig. 2) the original phenyl-(3-ketobutenyl)-sulphone gradually crystallized. The second ampoule was broken after exposure to ultra-violet light for 100 hr. The product was a yellow non-crystallizable oil, (infra-red spectra of the sample are given in Fig. 2) n_D^{20} 1·5560. (Found: C, 57·65, 57·40; H, 4·83, 4·89. $C_{10}H_{10}O_3S$ requires: C, 57·12; H, 4·72%). The 2,4-dinitrophenylhydrazone was obtained as yellow needles, m.p. 189–190° from ethyl acetate. (Found: N, 14·24. $C_{16}H_{14}N_4O_6S$ requires: N, 14·35%). A m.p. of a mixture with 2,4-dinitrophenylhydrazone produced from the starting sulphone showed a depression. The infra-red spectra of the 2,4-dinitrophenylhydrazone are shown in Fig. 1.

Cleavage of α-alkyl-α-(3-ketoalkenyl)-malonates in the presence of alkali. α-Alkyl-α-(3-ketoalkenyl)-malonate (0·12 mole) was gently refluxed for 30 min in a solution of potassium hydroxide

[20] H. J. Backer and A. E. Beute, *Rec. Trav. Chim.* **54**, 167 (1935).

VOL. 12 1961

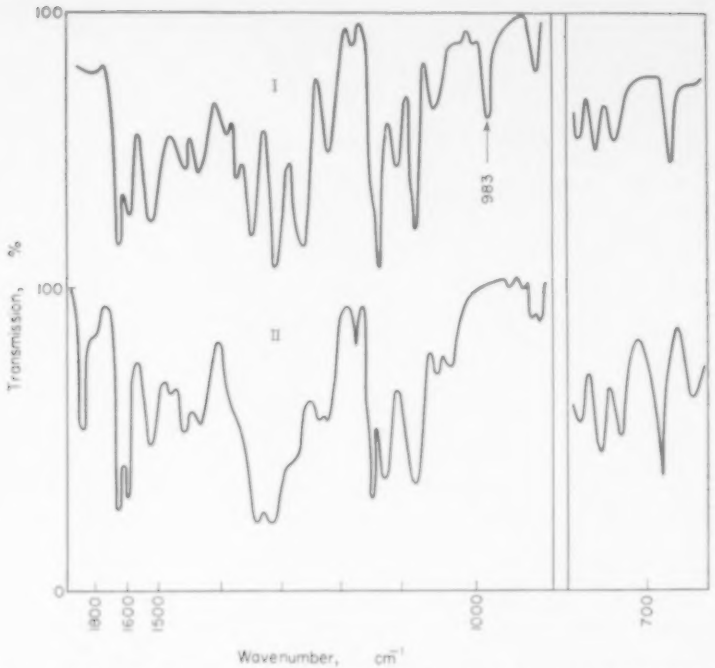


FIG. 1. Infra-red spectra: I—2,4-dinitrophenylhydrazone of *trans*-phenyl-(3-ketobutenyl)-sulphone; II—2,4-dinitrophenylhydrazone of *cis*-phenyl-(3-ketobutenyl)-sulphone.

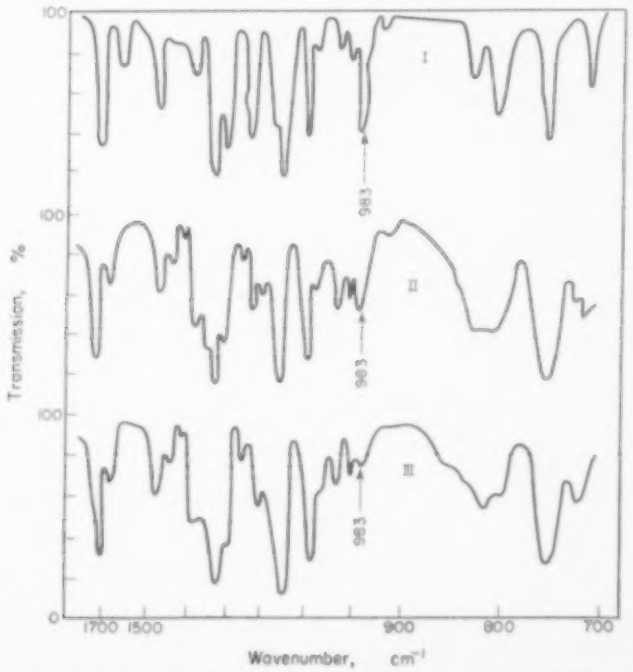


FIG. 2. Infra-red spectra: I—*trans*-phenyl-(3-ketobutenyl)-sulphone; II and III—sulphone after action of ultra-violet light for 50 and 100 hr respectively.

(26·5 g) dissolved in the minimum of water. After 1 hr it was filtered, the filtrate evaporated *in vacuo*, 200 cc water added, acidified with 10% hydrochloric acid to pH 3–4, extracted with ether, the ether removed and the residue distilled *in vacuo*. Yields, constants, and analyses of compounds obtained are listed in Table 9.

TABLE 9. R-COCH—CHR′CO_2CH_3

N°	R	R′	Yield %	b.p.	d_4^{20}	n_D^{20}	MRD		% C		% H	
							Found	Calc.	Found	Calc.	Found	Calc.
1	CH_3	C_2H_5	63	104–105/6 mm	1·0210	1·4625	45·87	44·96	63·63 63·75	63·51	8·18 8·28	8·29
2	CH_3	C_3H_7	60	105–106/5 mm	1·0033	1·4605	50·33	49·58	65·48	65·19	8·90	8·75
3	C_2H_5	C_3H_7	94	111–112/4 mm	0·9944	1·4683	55·45	54·20	66·50 66·62	66·64	9·08 9·11	9·15
4	C_7H_{15}	C_2H_5	63	145/1 mm	0·9508	1·4638	77·86	77·29	71·87 71·79	71·60	10·54 10·56	10·52

Cleavage of α-alkyl-α-(3-ketoalkenyl)-acetoacetates with aqueous ammonia

Ethyl α-(3-ketobutenyl)-butyrate. Ammonium chloride (32 g) was dissolved in water (150 cc), aqueous ammonia (34 cc, *d* 0·9) added, the solution heated to 45° and poured into α-ethyl-α-(3-ketobutenyl)-acetoacetate (56·4 g, 0·25 mole). The reaction was carried out with stirring for 15–17 min at 50–55°, then cooled to room temp. An oil separated, the water layer was extracted with ether, the solvents removed and the residue distilled *in vacuo*. Other α-ethyl-α-(3-ketoalkenyl)-acetoacetates were cleaved in a similar manner, an optimum ammonia concentration being chosen for each particular case. Yields, constants and analyses of compounds obtained are listed in Table 10.

TABLE 10. RCOCH—CHCHR′$CO_2C_2H_5$

R	R′	b.p.	d_4^{20}	n_D^{20}	Yield	Analyses	
						Found	Calc.
CH_3	C_2H_5	85–88°/1 mm	1·0058	1·4560	70%	C, 64·96, 64·92 H, 8·78, 8·95	C, 65·19 H, 8·75
C_2H_5	C_2H_5	88–91°/1 mm	0·9907	1·4562	70%	C, 66·27, 66·43 H, 9·27, 9·14	C, 66·64 H, 9·15
C_3H_7	C_2H_5	92–94°/1 mm	0·0726	1·4561	41·5%	C, 67·85, 67·89 H, 9·68, 9·61	C, 67·89 H, 9·50

TABLE 11. RCOCH—CHCH(CH_3)$COCH_3$

R	b.p.	d_4^{20}	n_D^{20}	Yield	Analyses	
					Found	Calc.
CH_3	74–75·5°/1 mm	0·9979	1·4756	76·5%	C, 68·54 H, 8·63	C, 68·22, 68·45 H, 8·52, 8·62
C_2H_5	82–83°/1 mm	0·9809	1·4748	76·5%	C, 70·10 H, 9·15	C, 69·92 H, 9·38
C_3H_7	87–88·5°/1 mm	0·9648	1·4723	81·5%	C, 71·39 H, 9·59	C, 71·22, 71·44 H, 9·60, 9·89

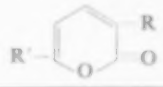
Unsaturated δ-diketones. To potassium hydroxide solution (0·13 mole) in water (65 cc) methyl-(3-ketoalkenyl)-acetylacetone (0·06 mole) was added, the mixture being stirred at 10–15° for 20 min, the undissolved oil extracted with ether, and the remaining solution acidified with 50% sulphuric acid. An oil separated, the water layer was extracted with ether, the ether removed and the residue distilled in a nitrogen atmosphere *in vacuo*. The constants, yields, and analyses of compounds obtained are listed in Table 11.

3,6-Disubstituted, α-pyrones

Synthesis of 3,6-dialkyl-α-pyrones from α-ethyl-α-(3-ketoalkenyl)-acetoacetates. α-Ethyl-α-(3-ketoalkenyl)-acetoacetate (0·16 mole) was refluxed for 3½ hr with a mixture of conc hydrochloric (80 cc) and glacial acetic acids in amounts necessary to keep the reaction mixture homogeneous. The mixture was then poured into water, (150–200 cc), the oil separated, the water layer extracted with ether, the ether removed, and the residue distilled *in vacuo*. The constants, yields, and analyses of compounds obtained are listed in Table 12. 3,6-Disubstituted pyrones are formed under similar conditions from ketovinylation products of cyclic-β-ketoacids. Thus, for example, 1-carbethoxy-1-(3-ketohexenyl)-cyclopentanone-2 gives ω-(6-propyl-α-pyronoyl-3)-butyric acid in 56% yield, the constants and analyses being listed in Table 12.

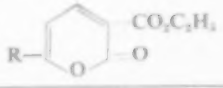
6-Alkyl-3-carbethoxy-α-pyrones. 3-Ketoalkenylmalonate (0·03 mole) was refluxed for 2 hr with acetyl chloride (5 cc), the 6-alkyl-3-carbethoxy-α-pyrone produced being isolated either by precipitation with petroleum ether or distillation. The yields, constants, and analyses of compounds obtained are listed in Table 13.

TABLE 12.



R′	R	b.p.	d_4^{20}	n_D^{20}	Yield	Analyses	
						Found	Calc.
CH_3	C_2H_5	87–88°/1 mm	1·0643	1·5168	71%	C, 69·54 H, 7·29	C, 69·56, 69·68 H, 7·48, 7·43
C_2H_5	C_2H_5	74–76°/1 mm	1·0492	1·5105	67·5%	C, 71·02 H, 7·95	C, 70·85, 70·76 H, 8·02, 8·11
C_3H_7	C_2H_5	79–81°/1 mm	1·0167	1·5060	71%	C, 72·26 H, 8·48	C, 72·43, 72·51 H, 8·79, 8·72
C_3H_7	$(CH_2)_2COOH$	195–202°/2 mm	—	1·5232	56%	C, 64·28 H, 7·19	C, 64·70, 64·75 H, 7·43, 7·48

TABLE 13.



N°	R	Yield %	m.p.	b.p.	d_4^{20}	n_D^{20}	% C		% H	
							Found	Calc.	Found	Calc.
1	CH_3	53	86°	—	—	—	59·24 59·19	59·34	5·30 5·46	5·53
2	C_2H_5	92	—	162–163/7 mm	1·1767	1·5265	60·95 60·88	61·21	6·38 6·40	6·17
3	C_3H_7	68	—	164–166/6 mm	1·1285	1·5770	62·88 62·95	62·84	6·83 6·88	6·71

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TRANS-ENOLIZATION

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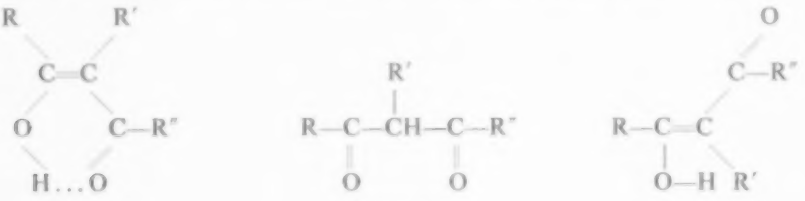
Abstract—The solvent effect on *trans*-enolization of different keto-enols is discussed. Ultra-violet and infra-red data are presented on keto–enol equilibrium in α-alkyltetronic acids, isopropylidene alkyl malonates, and α-alkyl-substituted alkyl acetoacetates, bromometrical evidence also being produced for the latter compounds. The limitations of Meyer's rule and Eistert and Reiss' hypothesis as to *trans*-enolization are shown and the general applicability of the relationship $K_T = EL + E'L'$ is demonstrated.

1. GENERAL CONSIDERATIONS

IT has been established that solutions of β-dicarbonyl compounds with open chains generally contain at least the ketonic, *cis*- and *trans*-enolic forms in equilibrium.[1]



Cis-enol Ketone *Trans*-enol

This equilibrium of the three forms is determined by their ionization constants in a particular solvent, i.e. depends upon the acidic properties of the forms and their solvation.[2]

The enolic forms of ethyl acetoacetate and other related keto-enols are considered as chelated hydrogen bonded *cis*-forms.[3,4] Contrary to ketonic forms, they have a comparatively low boiling point and are more readily soluble in non-polar (hydrophobic) than in polar (hydrophilic) solvents. Hence, in full accordance with the Van't Hoff–Dimrot's rule,[5] the non-polar solvents shift the tautomeric equilibrium toward the enolic (*cis*-)forms and the polar solvents toward the ketonic forms. These relationships are expressed by the well known Meyer's equation[6] $K_T = EL$ where K_T is the keto-enol equilibrium constant of any keto-enol in solution, E is the enolizability of the keto-enol independent of the solvent, L is the enolizing capacity of the solvent equal to the equilibrium constant of the standard compound such as ethyl acetoacetate ($E = 1$). The value L changes from $4 \cdot 10^{-3}$ for water to 1 for hexane. The graphic dependence of K_T on L for keto-enols obeying Meyer's equation is shown by straight lines passing through the origin.

* Translated by A. L. Pumpiansky, Moscow.

[1] B. Eistert, F. Arndt and E. Ayça, *Chem. Ber.* **84**, 156 (1951).
[2] M. I. Kabachnik, *Izv. Akad. Nauk* 98 (1955).
[3] N. V. Sidgwick, *J. Chem. Soc.* **127**, 907 (1925).
[4] P. Nachod, *Z. Phys. Chem.* **A.182**, 208 (1938).
[5] O. Dimroth, *Liebigs Ann.* **377**, 134 (1910); **399**, 93 (1913).
[6] K. H. Meyer, *Ber. Dtsch. Chem. Ges.* **45**, 2846 (1912); **47**, 826 (1914).

The case becomes complicated when a considerable amount of *trans*-enolic form appears together with the *cis*-enolic form in the solution as first exemplified with ethyl formylphenylacetate.[7]

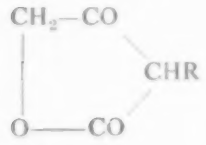
Henecka[8] has reported on a number of *trans*-enolic forms accounted for by their failing to give a colour reaction with ferric chloride. These compounds are found to deviate from Meyer's rule.

Trans-enolization was first discussed in detail by Arndt *et al.*[9] These authors found it controversial that hydrophilic solvents shift the tautomeric equilibrium toward the ketonic form rather than toward the most polar *trans*-enolic form containing an open hydroxyl group.

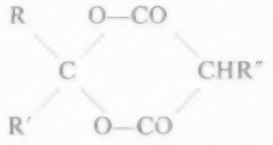
The authors answered the question "Warum nicht *trans*-Enol?" by assuming that the ketonic forms produce highly polar hydrates and semiacetals which react as ketonic forms. There are objections to this hypothesis[2,10] which is also invalid when investigating the effect of pressure on keto-enol equilibrium.[11]

Eistert and Reiss[12] have studied cyclic keto-enols containing both carbonyl groups in the same ring and hence unable to produce *cis*-enolic forms but producing "*trans*-fixed" enols. These authors consider that the effect of the solvent on keto-*trans*-enol equilibrium is opposite to Meyer's rule, i.e. the hydrophilic solvents must shift the equilibrium toward the enolic forms and the hydrophobic solvents toward the ketonic forms. The bromometrical analysis of solutions of such keto-enols in different solvents gave rather inaccurate and not easily reproducible results but did in general confirm the hypothesis.

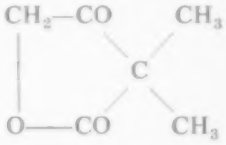
Thus in solutions of α-methyltetronic acid (I) in ether, methanol and water the percentage of enol amounted to 69, 97 and 100 whilst cyclic isopropylidene malonate (IV) ("Meldrum's acid") in benzene, methanol and water showed 37, 95 and 128 per cent, respectively.



I $R = CH_3$
II $R = C_2H_5$
III $R = C_3H_7$



IV $R = R' = CH_3$; $R'' = H$
V $R = R' = CH_3$; $R'' = C_2H_5$



VI

This hypothesis has been proved spectrometrically for a number of other cases, but it does not agree with the spectrometric data on α-ethyltetronic acid (II) obtained by other workers[13,14] as cited in the same paper. This hypothesis is, however, in accordance with ultra-violet evidence obtained by Russel[15] who found that solutions of β-cyanoketones whose enolic forms are sterically unable to exist as chelates and thereby

[7] W. Dieckmann, *Ber. Dtsch. Chem. Ges.* **50**, 1376 (1917).
[8] H. Henecka, *Chem. Ber.* **81**, 192 (1948).
[9] F. Arndt, L. Loewe and R. Ginkök, *Rev. Fac. Soc. Istanbul* **A11**, 147 (1946).
[10] G. Brigleb and W. Strohmeyer, *Angew. Chem.* **64**, 409 (1952).
[11] M. I. Kabachnik, S. E. Yakushkina and N. B. Kislyakova, *Dokl. Akad. Nauk SSSR* **96**, 1169 (1954).
[12] B. Eistert and W. Reiss, *Chem. Ber.* **87**, 92 108 (1954).
[13] L. A. Dunkanson, *J. Chem. Soc.* 1210 (1953).
[14] R. W. Herbert and E. L. Hirst, *Biochem. J.* **29**, 1884 (1953).
[15] P. B. Russel, *J. Amer. Chem. Soc.* **74**, 2654 (1952).

contain an open hydroxyl group,[16,17] have more enolic forms in hydroxyl containing solvents than in hydrophobic ones. The data recorded by Russel were found to be much more involved. In the series of hydroxyl containing solvents such as water–methanol–ethanol–pentanol the enol content increases as the hydrophilic property of the solvent decreases. It reaches its maximum in pentanol, decreases in ether (yet remaining higher than in water), and then sharply drops in ether and hexane mixtures, being the lowest in hexane. This effect of the hydrophilic property of solvents cannot be accounted for either by Meyer's rule or the hypothesis under discussion.

Kabachnik[2] has considered the keto-*cis*-*trans*-enol equilibrium as acid–base equilibrium of three acids forming common anions. This equilibrium is in accordance with the acid-base equilibrium as formulated by Brønsted–Izmailov.[18–22] In solutions of keto-enols with an open chain both *cis*- and *trans*-enolic forms are present. The *trans*-enolic forms possess, however, considerably higher acidic properties. Therefore, their relative amount is always small and the keto-enol equilibrium is in agreement with Meyer's equation. But in polar solvents which dissolve the *trans*-form more readily, the overall decrease in enol content (at the expense of *cis*-enol) is accompanied by a relative increase of the *trans*-enolic form in the enolic fraction of keto-enol. Thus the discrepancy encountered by Arndt is explained.

In a more recent report on this subject[23] it has been shown that the effect of the solvent on the keto-*cis*-*trans*-enol equilibrium can be quantitatively accounted for in terms of an extended formula similar to that of Meyer but taking into consideration *trans*-enolization.

$$K_T = EL + E'L' \tag{1}$$

In this formula E and E' is the enolizability of keto-enol toward *cis*-enol (i.e. Meyer's constant) and *trans*-enol respectively; and L and L' is the enolizing capacity of the solvent toward *cis*-enol (L of Mayer) and *trans*-enol respectively. This relationship has been derived, like the Meyer's equation,[24] from the equation of Brønsted–Izmailov and is based on the assumption that the acid-base equilibrium theory is applicable to ketonic and *cis*- and *trans*-enolic forms as acids.*

To apply this formula, standard compounds must be chosen, one for *cis*-enolization ($E' = 0$; $E = 1$) and another for *trans*-enolization ($E = 0$; $E' = 1$). Ethyl acetoacetate may be used for *cis*-enolization, but the choice of a standard compound for *trans*-enolization is more difficult. Bromometrical[23] and spectrometric[25] investigation of the effect of the solvent on enolization of α-substituted acetoacetates described by Henecka[8] has shown that substances capable only of *trans*-enolization are characterized by a tautomeric equilibrium constant practically independent of the solvent. On the

* In formula (1) the parameters of L and L' remain constant in compounds of the same chemical type as this formula has been derived from $pK_{AS_1} = pK_{AS_2} + C$ with C is constant for acids of the same type.[20–21]

[16] S. B. Hendricks, O. R. Wulf, G. E. Hilbert and U. Liddel, *J. Amer. Chem. Soc.* **58**, 1991 (1936).
[17] G. S. Skinner, I. A. Gladner and R. F. Heitmiller, *J. Amer. Chem. Soc.* **73**, 2230 (1951).
[18] I. N. Brønsted, *Chem. Rev.* **5**, 291 (1928).
[19] I. N. Brønsted, *Z. Phys. Chem.* **A169**, 32 (1934).
[20] N. A. Ismailov, *Z. Phys. Chim. U.S.S.R.* **23**, 639, 643 (1949).
[21] N. A. Ismailov, *Z. Phys. Chim. U.S.S.R.* **24**, 321 (1950).
[22] N. A. Ismailov, *Izv. Univers. Kharkov* **10**, 5 (1953).
[23] M. I. Kabachnik, S. T. Yoffe and K. V. Vatsuro, *Tetrahedron* **1**, 317 (1957).
[24] M. I. Kabachnik, *Dokl. Akad. Nauk SSSR* **83**, 407, 859 (1952).
[25] M. E. Movsesyan, M. I. Kabachnik, S. T. Yoffe and K. V. Vatsuro, *Izv. Akad Nauk* (*Physical Series*) **22**, 1126 (1958).

other hand, the greater the *cis*-enolizability of the keto-enol, the more this constant depends on the solvent. Thus, for ethyl α-s-butylacetoacetate whose *cis*-enolic form is strongly hindered due to steric effects, the amount of enolic form proved to be practically constant in benzene, ethanol, methanol and 67 per cent aqueous methanol. This shows that for *trans*-enolization of such keto-enols, L' is practically constant and equation (1) may be more simply expressed as:

$$K_T = EL + E_1 \tag{2}$$

E_1 is a constant value denoting the *trans*-enolizability of α-substituted alkyl acetoacetates in any solvent. This conclusion is apparently substantiated by bromometrical estimation of the amount of enolic forms in solutions of some cyclic "*trans*-fixed" keto-enols carried out by the reversed Meyer's method.[23,*] The amount of *cis*- and *trans*-enolic forms in solutions of several α-substituted alkyl acetoacetates in various solvents may be calculated by application of formula (2).

The spectrometric investigation of enolization of some "*trans*-fixed" keto-enols was recently published by Eistert and Geiss.[26] Their results do not agree with the bromometric estimation of the amount of enolic forms in solutions of strongly acidic keto-enols determined by us[23] and by Eistert and Reiss.[12]

Thus, for example, in bromometric determinations,[12] isopropylidene malonate (IV) is 37–128 per cent enolized in different solvents and isopropylidene ethyl malonate (V) contains about 70 per cent of enol, whereas actually no enol form is present. As spectrometric data is regarded as more reliable in these cases it may be concluded that the bromometric method cannot be applied to these compounds. It is suggested that the bromometric method is unsuitable for strongly acidic cyclic β-dicarbonyl compounds as in addition to the bromination of anion there may be fast direct bromination of the ketonic form.†

Thus, it is necessary to consider:

(1) The actual effect of solvents on enolization of different "*trans*-fixed" cyclic keto-enols and the extent to which the hypothesis advanced by German authors on the reversion of Meyer's rule can be applied.

(2) The effect of solvents on *trans*-enolization of open chain ketones, the extent to which formula (2) is valid, and the substance which may be used as standard compounds for *trans*-enolization of β-keto esters.

These considerations led to additional experimental investigation which gave the following results.

2. RESULTS

α-Alkyltetronic acids

According to Eistert and Geiss[26] in solutions of α-ethyltetronic acid (II) and isoalkylidene malonates (IV) and (V) the only equilibrium observed is between ketonic forms and the corresponding enolate anion. The observed overlapping of ultra-violet absorption spectra of ethyltetronic acid in water, methanol and ethanol is explained by

* In the work cited direct bromometrical titration procedure was mistakenly mentioned as applied for these compounds.

† On direct titration of benzene solution V and solution III in aqueous methanol with bromine solution in methanol or ethanol the amount of bromine consumed corresponds to 100 per cent enol content.

[26] B. Eistert and F. Geiss, *Tetrahedron* **7**, 1 (1959).

Eistert and Reiss as being due to the occasional coincidence in the concentration of enolate anions in solutions investigated. No reference is made to the observations by Duncanson[13], Herbert and Hirst[14] and ourselves that the enolization of α-ethyl-tetronic acid is approximately constant in such different solvents as aqueous sulphuric acid and ethylene chloride.

We found that the infra-red spectra of crystalline α-ethyl- and propyl-tetronic acids (Fig. 1a and b) are markedly different at 1800 cm^{-1} and 2600 to 3000 cm^{-1} from those of the lactone of γ-hydroxy-α,α-dimethylacetoacetic acid (VI) of a similar structure but with fixed ketonic forms (Fig. 1c). In the spectrum of this lactone the 1745 and 1798 cm^{-1} bands definitely refer to the stretching vibrations of the ketonic and

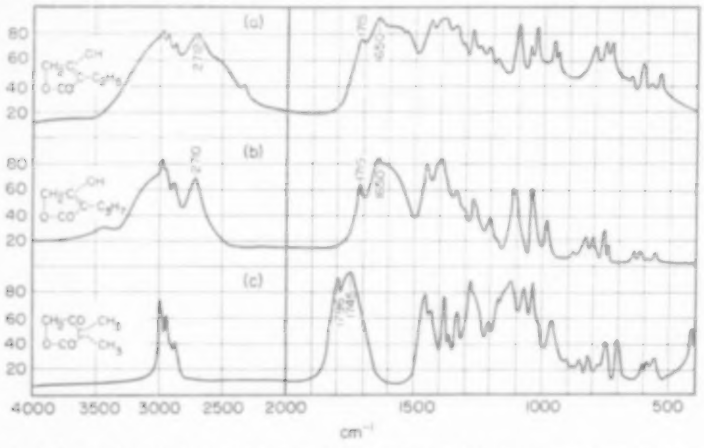


FIG. 1. Infra-red spectra of crystalline α-ethyl (a), α-propyl (b) tetronic acids and of lactone of γ-hydroxy-α-α-dimethylacetoacetic acid (c).

carbalkoxylic carbonyl.* Within the range of 2600–3300 cm^{-1} the spectrum of this compound reveals only characteristic C—H frequencies. The infra-red spectra of crystalline ethyl- and propyl-tetronic acids (II and III) showed a broad diffused band at 3050–2950 cm^{-1} and a sharp band at 2710 cm^{-1}. The character and position of these bands allow them to be assigned to the stretching vibrations of hydroxyl groups involved in intermolecular hydrogen bonds. The α-alkyltetronic acids under study have thus an enolic structure. This is in good agreement with the absorption bands of these compounds observed in the range of double bond stretching vibrations such as 1650 and 1715 cm^{-1}. The former band may be accounted for by the vibration of the C=C bond in the enolic form, the latter by that of the C=O bond.†

The lowering in the C=O frequency as compared to the vibration frequency of the

* Higher values of these frequencies as compared to those of similar vibrations of non cyclic β-dicarbonyl compounds seems to be due to the peculiarity of the five-membered ring. It is known,[27] that the stretching vibration frequencies of carbonyl groups in cyclic compounds involving C=O increase as the ring becoming more strained.

† The C=C and C=O stretching vibration frequencies in II and III are to be compared with those of substituted acryloates. Thus the latter spectra show the C=C stretching vibration frequencies to be at 1630–1650 cm^{-1} whilst those of C=O at 1715 to 1725 cm^{-1}.[28]

[27] V. Bellamy, *The Infra-red Spectra of Complex Molecules*. London (1954).
[28] R. W. F. Kohlrausch *Raman Spectren*. Leipzig (1943).

VOL. 12 1961

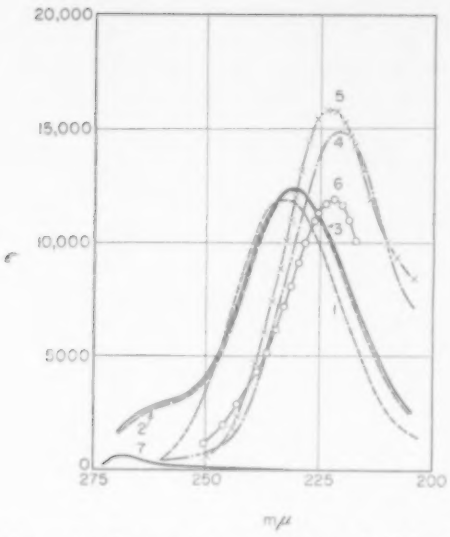


FIG. 2. Ultra-violet spectra of α-propyltetronic acid (conc. $5 \cdot 10^{-4}$ mole/l.) in different solvents such as (1) water (– – – –) at pH 2·50 (2) methanol (— — — —) (3) ethanol (————) (4) ether (————) (5) dioxan (—×—×—×—×—×—) (6) dichloroethane (o—o—o—o—o) (7) lactone of γ-hydroxy-α,α-dimethylacetoacetic acid in methanol.

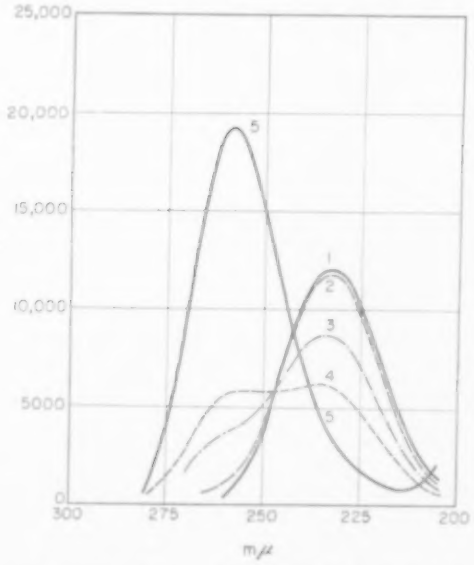


FIG. 3. Ultra-violet spectra of α-propyltetronic acid in water at different pH's (conc $5 \cdot 10^{-4}$ mole/l.): (1) pH 2·50 (2) pH 2·90 (3) pH 3·35 (4) pH 3·75 (5) pH 11.20.

carbalkoxyl of the lactone mentioned above (spectrum 1c) to 1798 cm^{-1} is accounted for by the intermolecular hydrogen bonding and conjugation.*

The ultra-violet spectra of α-propyltetronic acid were investigated in water (at pH 2·50, 2·90, 3·35, 3·75, and 11·20) in methanol, ethanol, ether, dioxan, and dichloroethane (Figs. 2 and 3), that of lactone (VI) in methanol (Figs. 2 and 4).

As will be seen from the absorption curves the ultra-violet spectra of α-propyltetronic acid and that of reference lactone (VI) of a ketonic structure are markedly

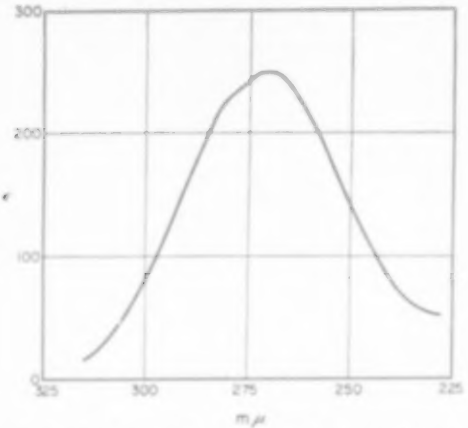


FIG. 4. Ultra-violet spectra of lactone of γ-hydroxy-α,α-dimethylacetoacetic acid in methanol (conc $5 \cdot 10^{-5}$ mole/l.)

different both as to their position and the intensity of absorption bands. Hence in solutions of α-propyltetronic acid the tautomeric equilibrium is not shifted toward the ketonic form. In aqueous solution at high pH (11·20) one observes only one intensive maximum at 258 mμ that undoubtedly is characteristic of the absorption of the anion of α-propyltetronic acid.[13,14] The lowering of pH results in decrease of the intensity of this maximum. In acidic media there appears a fairly intensive absorption maximum at 233 mμ, that can only be assigned to non-dissociated molecules of α-propyltetronic acid, as not corresponding in character to the ketonic form are, therefore, attributable to the enolic form.† Thus the changes in the ultra-violet spectra observed with changing pH characterize the ionic dissociation equilibrium of the enolic α-propyltetronic acid. As the ultra-violet absorptions in acidified water, methanol, and ethanol as previously reported,[29] practically coincide (Fig. 2), the extent of enolization in these as well as in dichloroethane solutions are almost the same. The concentration of enolic form is higher in ether and is further increased in dioxan. Due to low absorption intensity of ketonic forms in the ultra-violet the data obtained cannot be used to determine the tautomeric equilibrium constant. It is, however, clear that it does not depend on the solvent and its variation is not explained by the hypothesis suggested by Eistert and Reiss.

The ultra-violet evidence agrees with the infra-red data for 1 per cent solutions of

* Conjugation usually lowers the C=O frequency by 20–40 cm^{-1},[28] and hydrogen bonding by 50–60 cm^{-1}.[28,30] Simultaneous action of these factors can result in the overall lowering of C=O frequency down to 70–100 cm^{-1}.

† Absorption curves are reproducible whin passing back from acidic to basic solutions.

[29] R. S. Rasmussen and R. K. Brattain, *J. Amer. Chem. Soc.* **71**, 1077 (1949).

[30] R. S. Rasmussen, D. D. Tunnicliff and R. R. Brattain, *J. Amer. Chem. Soc.* **71**, 1068 (1949).

α-propyltetronic acid in chloroform, ether, tetrahydrofuran and saturated solutions in carbon tetrachloride (Fig. 5).

The spectrum of the solution in chloroform (Fig. 5b) reveals intensive bands at 1652 and 1730 cm^{-1}, which are similar to the corresponding bands of the crystalline compound and, therefore, are assigned to the enolic form. The spectra also show weak bands at 1768 and 1812 cm^{-1}, roughly corresponding to the frequencies of lactone (VI) and possibly accounting for the ketonic form. It can, therefore, be suggested

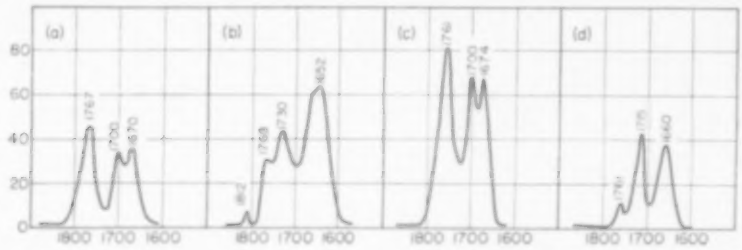


FIG. 5. Infra-red spectra of solutions of α-propyltetronic acid in (a) ether (b) chloroform (c) tetrahydrofurane (conc 1 per cent) (d) carbon tetrachloride (saturated solution).

that when the crystalline enolic form is dissolved in chloroform a minute amount of ketonic form is produced. Similarly, the spectrum of α-ethyltetronic acid in carbon tetrachloride solution (Fig. 5d) shows two enolic bands at 1650 and 1715 cm^{-1} and a band at 1761 cm^{-1} which may be assigned to the stretching C=O vibration of the ketonic form or to the C=O enol not involved in the hydrogen bonding. Its relative intensity is weaker than that of the corresponding band in chloroform solution and may be accounted for either by a lower content of the ketonic form or by a decrease in the number of molecules free from hydrogen bonding. Owing to poor solubility of the compound in carbon tetrachloride a fairly weak band at 1800 cm^{-1} assigned to the ketonic carbonyl was not observed. The spectrum of α-ethyltetronic acid in carbon tetrachloride has been described by Duncanson[12]. Besides the three bands mentioned, he observed a band at 1818 cm^{-1}, which supports the conclusion concerning the presence of ketonic forms in solutions of α-alkyltetronic acid in chloroform and carbon tetrachloride.

The infra-red spectra of α-propyltetronic acid in ether and tetrahydrofuran (Fig. 5a and c) reveal three sharp bands at 1670, 1700, and 1760 cm^{-1}. It appears that the first may be assigned to the stretching vibration of C=C, and the second to C=O of the enolic form (hydrogen bonds). Concerning the 1760 cm^{-1} band, it may be assigned either to the C=O of the ketonic form, or to the hydrogen bond free enolic carbonyl. The second explanation is more acceptable as the presence of a ketonic form should produce a band at 1800 cm^{-1} which is not the case. The infra-red evidence confirms the existence of enolic α-propyltetronic acid in solution and one may reasonably expect the presence of a small amount of the ketonic form in the chloroform or carbon tetrachloride solutions.

Isopropylidene ethyl malonate

The infra-red spectrum of crystalline isopropylidene ethyl-malonate (V, Fig. 6a) reveals intensive absorption at 1740 to 1775 cm^{-1} corresponding to characteristic

C—O vibrations of ketonic carbonyls and carbalkoxyls. The ketonic structure of the crystalline molecules is also confirmed by the absence of hydroxyl absorption bands. The spectrum of this acid in carbon tetrachloride solutions shows a sharp line at 3535 cm^{-1} [31] which may be assigned either to free hydroxyl vibrations, indicating the presence of the enolic form, or to the C—O stretching vibration overtone. In the spectrum of the monodeuterated derivative in solution, the 3535 cm^{-1} line remains unchanged substantiating the latter suggestion. The isotopic substitution occurs at the

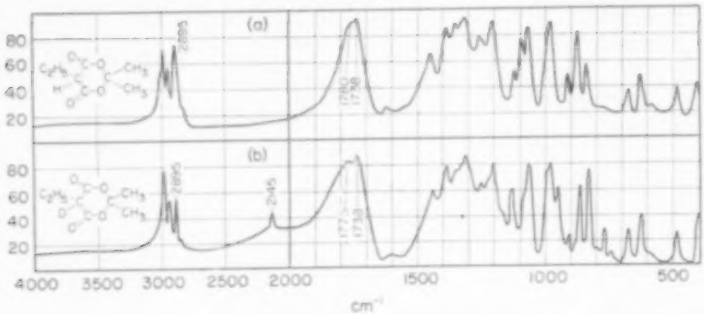


FIG. 6. Infra-red spectra of crystalline isopropylidene ethylmalonate (a) and isopropylidene monodeuteroethylmalonate (b).

ketonic α-carbon as evidenced by a marked decrease in the intensity of the band at 2895 cm^{-1}, as compared with the non-deuterated compound, and by the appearanee of a band at 2145 cm^{-1} (Fig. 6b).

The ultra-violet spectra of alkaline, neutral and acidic methanol solutions of isopropylidene ethyl malonate (Fig. 7) are similar to that observed by Eistert and Geiss[26]

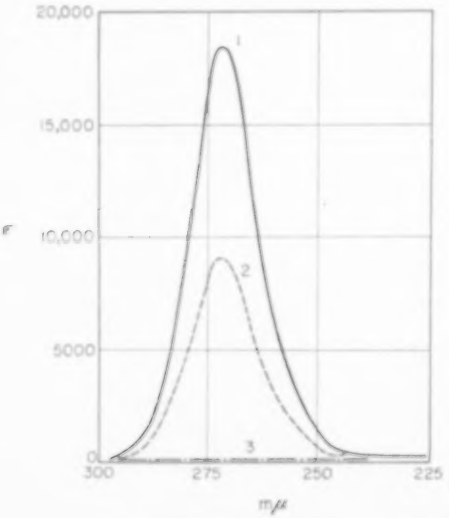


FIG. 7. Ultra-violet spectra of isopropylidene ethylmalonate in alkaline (1), neutral (2), and acidic (3) methanol.

[31] M. E. Movsesyan, Dissertation, Moscow (1959).

in the spectra of its *spyro* analogs. In the alkaline solution an intensive absorption with a maximum of 272 mμ is observed, this is weaker in the neutral solution and non-existent in the acidic solution, but the maximum is again reached on addition of the required amount of alkali. In agreement with the German authors, this evidence shows that the ketonic form only is present in the crystalline state or when dissolved in non-polar solvents. In polar solvents the ketonic form is in equilibrium with the enolate anion, the concentration of which depends on the acidity of the

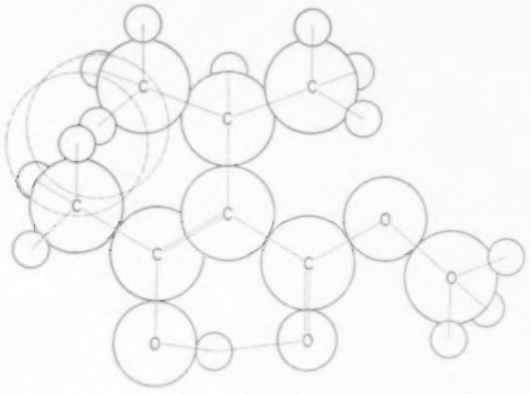


FIG. 8. *Cis*-enolic form of ethyl α-isopropylacetoacetate.

medium. Under no conditions do these cyclic β-dicarbonyl compounds enolize and, therefore, do not obey either Meyer's rule or the hypothesis of Eistert and Reiss.

Alkyl α-alkylacetoacetates

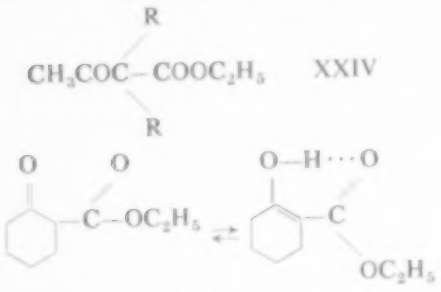
Esters with α-alkyl substituents such as s-butyl-(XVI), cyclopentyl-(XXII), 2-pentyl-(XVIII), 3-pentyl-(XVII), 2-hexyl-(XIX), and 2-heptyl-(XX) were spectroscopically investigated. In all these compounds the appearance of a planar *cis*-enol form with intramolecular hydrogen bonding is accompanied by strong steric hindrance due to the overlapping of α-alkyl- and γ-methyl-groups (cf. Henecka[8]). This is shown in Fig. 8 which roughly pictures the relationships.

When considering the infra-red data for these compounds, particular attention was paid to the assignment of frequencies of different tautomeric forms.

The α,α-disubstituted acetoacetates (XXIV), with "fixed" ketonic forms have spectra with two intensive bands over the range of 1710–1730 cm^{-1} and 1740–1760 cm^{-1}, which are assigned to C═O carbonyls and carbalkoxyls, respectively.[28] In the spectra of *cis*-fixed ketoenols such as those of cyclohexanone- (or cyclopentanone-)carboxylates (XXV) four bands are observed in the 1600–1800 cm^{-1} range.[25] Two of them are within the frequency range of 1710–1730 cm^{-1} and 1740–1760 cm^{-1} and are assigned to the ketonic isomer. Two other bands at 1610–1630 cm^{-1} and 1650–1660 cm^{-1} may refer to the enolic form, inasmuch as their intensity increases with increasing enolizing capacity of the solvent, and at the same time the band intensity of the ketonic form decreases.[25,30,31] The weaker absorption band at 1610–1630 cm^{-1} is assigned to the stretching vibration of the C═C bond and the intensive band at

$$CH_3COCHCOOC_2H_5$$
$$\quad\quad|$$
$$\quad\quad R$$

VII	$R=CH_3$	XIV	$R=i\text{-}C_3H_7$	XXI	$R=C_6H_{13}(CH_3)CH$
VIII	$R=C_2H_5$	XV	$R=i\text{-}C_4H_9$	XXII	$R=\text{cyclo-}C_5H_9$
IX	$R=n\text{-}C_3H_7$	XVI	$R=s\text{-}C_4H_9$	XXIII	$R=\text{cyclo-}C_6H_{11}$
X	$R=n\text{-}C_4H_9$	XVII	$R=(C_2H_5)_2CH$		
XI	$R=n\text{-}C_7H_{15}$	XVIII	$R=C_3H_7(CH_3)CH$		
XII	$R=C_6H_5$	XIX	$R=C_4H_9(CH_3)CH$		
XIII	$R=C_6H_5CH_2$	XX	$R=C_5H_{11}(CH_3)CH$		



XXIV

XXV

1650–1660 cm^{-1} to the C=O vibration of the carbalkoxy group involved in intramolecular hydrogen bonding and conjugated with the double bond.

The infra-red spectra of α-alkylacetoacetates (Fig. 9) show three bands over the range of 1600–1750 cm^{-1}, their frequencies and assignment are given in Table 1.

The absence of absorption bands within 1650–1660 cm^{-1} characteristic of *cis*-configuration points to the *trans*-enolization of these compounds. The presence of

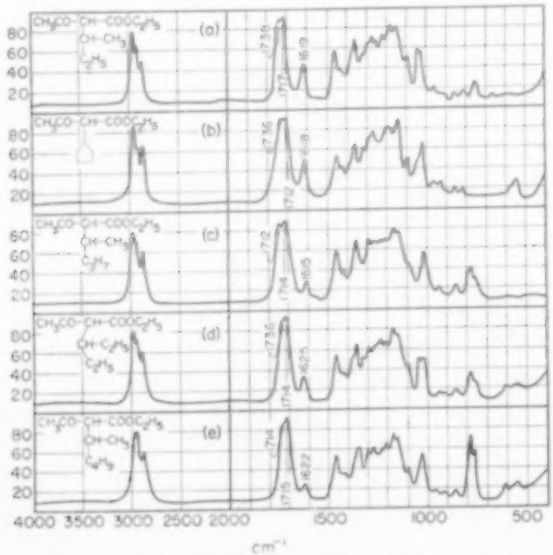


FIG. 9. Infra-red spectra of ethyl α-alkylacetoacetates.

TABLE 1. ASSIGNMENT OF FREQUENCIES OVER THE RANGE OF 1600–1800 cm^{-1} TO THE VIBRATION OF BONDS OF C=O AND C=C TAUTOMERIC FORMS OF ETHYL α-ALKYL ACETOACETATES

Compound	Ketonic form		Enolic form
$CH_3COCHRCOOC_2H_5$	I Carboxyl $\nu C=O$	II Carbonyl $\nu C=O$	III $\nu C=C$
R = Sec-C_4H_9	1738	1717	1619
R = cyclo-C_5H_9	1736	1712	1618
R = $C_2H_7(CH_3)CH$—	1742	1718	1615
R = $(C_2H_5)_2CH$—	1738	1714	1625
R = $C_4H_9(CH_3)CH$	1738	1715	1622

enolic forms in *trans*-configuration is confirmed by the lack of a marked colour reaction with ferric chloride. The spectra exhibit no separate absorption band corresponding to C=O enolic forms which should appear in the 1700–1730 cm^{-1} range and are suppressed by intensive absorption bands of ketonic forms, the content of which was bromometrically shown to exceed considerably that of enolic forms. The ready solubility of alkyl-α-alkyl acetoacetates in various solvents permits the quantitative estimation of enolization and elucidates the solvent effect on these compounds.

As in the case of ethyl acetoacetate,[25] the solvents do not affect the molar absorption coefficient ratio of tautomeric forms within the accuracy of the experiment. In this case the ratio of optical densities of absorption bands of two tautomeric forms in infra-red spectra of solutions is proportional to the tautomeric equilibrium constant. In Fig. 10 the ratio (D III/D II) of optical densities of III(enolic) to II(ketonic) (Table 1) is plotted against the constant *L* (Meyer[6]) of the enolizing capacity of solvents. It is seen from Fig. 10 that in α-alkylsubstituted acetoacetate derivatives with branched alkyl groups, the content of enolic forms is essentially independent of the solvent. This agrees with the ultra-violet evidence obtained relating to the effect of such different polar solvents as water, alcohols, ether, and hexane. In Fig. 11 the ultra-violet spectra of ethyl-α-s-butylacetoacetate (XVI) solutions in acidified 67 per cent aqueous methanol (pH 2·5), methanol, ethanol, ether, and hexane are given. All curves agree well in intensity ($\varepsilon \cong 2000$) and have a maximum at 233 to 240 mμ. *Trans*-enolization of keto-enols with an open chain is, therefore, independent, as far as α-alkylsubstituted acetoacetates are concerned, of the nature of the solvent, and

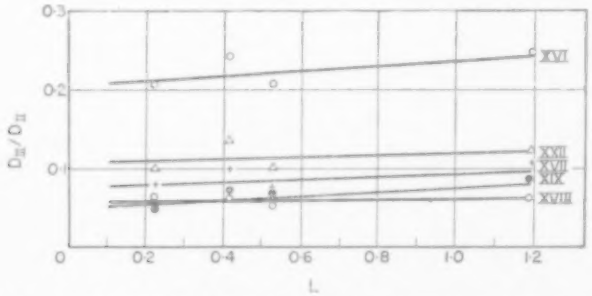


FIG. 10. A plot of D III/D II (optical densities of enolic and ketonic forms of ethyl α-alkyl-acetoacetates with branched substituents) against L.

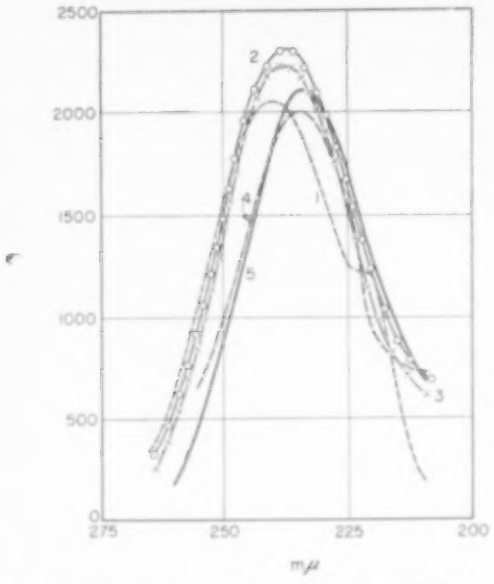


FIG. 11. Ultra-violet spectra of ethyl α-s-butylacetoacetate in (1) 67 per cent aqueous methanol at pH 2·50 (. . . . .) methanol (—o—o—o—o—o) (3) ethanol (×—×—×—×—×—) (4) hexane (— — — —) (5) ether (————).

does not accord with either Meyer's rule or Arndt–Eistert and Reiss' hypothesis. The spectral data obtained fully coincide with direct bromometrical determination of the amount of enolic forms contained in different α-alkylacetoacetates. The compounds investigated are all weak acids and so the bromometrical procedure affords reliable results. In Tables 2, 3, and 4 the values obtained for esters with branched substituents together with those for esters with other alkyl and aryl substituents are listed.

TABLE 2. ENOL PERCENTAGE IN α-SUBSTITUTED ETHYL ACETOACETATES IN DIFFERENT SOLVENTS

Substituent R in $CH_3COCHRCOOC_2H_5$	Solvent					
	67%-CH_3OH	CH_3OH	C_2H_5OH	C_6H_6	$(C_2H_5)_2O$	CCl_4
C_2H_5	0·9	1·8	2·8	4·2		
n-C_3H_7	1·9	3·0	4·2	5·6		
n-C_4H_9	3·4	4·3	5·4	6·2		
n-C_5H_{11}	3·6	4·9	6·0	7·0		
iso-C_3H_7	2·6	3·0	3·1	3·6		
iso-C_4H_9	3·3	4·7	6·7	7·9		
s-C_4H_9	14·3	14·5	13·9	14·6		14·8
$(C_2H_5)_2CH$	6·2	6·7	7·2	8·0	9·3	
n-$C_3H_7(CH_3)CH$—	3·9	4·1	4·3	5·1	6·1	7·2
n-$C_4H_9(CH_3)CH$—	4·5	4·7	4·8	4·9	5·8	6·2
n-$C_5H_{11}(CH_3)CH$—	3·8	3·9	4·1	4·4		
n-$C_6H_{13}(CH_3)CH$—	3·9	4·5	4·4	4·7		
Cyclohexyl	1·7	1·6	2·3	3·1		
Cyclopentyl	10·9	11·7	11·7	12·1		11·6
$C_6H_5CH_2$	1·6	3·2	5·0	7·9		

TABLE 3. ENOL PERCENTAGE IN α-SUBSTITUTED ETHYL ACETOACETATES IN DIFFERENT SOLVENTS

Substituent R in $CH_3COCH(R)COOC_2H_5$	Solvent									
	67% CH_3OH	CH_3CO-OH	CH_3OH	$CHCl_3$	C_2H_5OH	CH_3CO-OC_2H_5	C_6H_6	$C_6H_5CH_3$	$(C_2H_5)_2O$	CCl_4
H	2·0	5·7	7·1	8·3	11·4	13·0	18·3	21·0	29·1	34·6
CH_3	1·1		2·5		3·9	4·0	5·2	9·0		
C_6H_5	8·4	22·5	19·0	32·0	26·0	40·1	51·5	56·1		68·9

TABLE 4. *Cis*-ENOL PERCENTAGE IN THE ENOLIC FRACTION OF α-SUBSTITUTED ETHYL ACETOACETATES IN DIFFERENT SOLVENTS

Substituent R in $CH_3COCHRCO$-OC_2H_5	E	E_1	Solvent						Reaction* with FeCl
			67% CH_3OH	CH_3OH	C_2H_5OH	C_6H_6	$(C_2H_5)_2O$	CCl_4	
CH_3	0·319	−0·001	100	100	100	100			+ +
C_2H_5	0·177	0·005	46·6	74·8	83·1	89·5			+ +
n-C_3H_7	0·201	0·015	25·1	51·1	63·4	75·0			+ +
n-C_4H_9	0·156	0·033	10·6	26·9	37·9	51·5			+ +
n-C_7H_{15}	0·187	0·036	11·3	39·0	40·1	53·2			−
iso-C_3H_7	0·050	0·026	4·6	13·0	19·9	30·1			+
iso-C_4H_9	0·267	0·030	18·1	41·2	53·7	66·8			+
s-C_4H_9	0·016	0·165	0·3	0·8	1·3	2·2		5·0	−
$(C_2H_5)_2CH$—	0·097	0·065	3·5	10·4	16·1	25·1	37·9		+
n-$C_3H_7(CH_3)CH$—	0·072	0·037	4·5	15·5	20·1	30·4	44·4	50·7	−
n-$C_4H_9(CH_3)CH$—	0·037	0·046	2·0	5·9	9·4	15·5	24·7	29·9	−
n-$C_5H_{11}(CH_3)CH$—	0·035	0·038	2·2	6·8	10·6	17·1			−
n-$C_6H_{13}(CH_3)CH$—	0·039	0·041	1·9	7·0	11·0	17·7			−
Cyclohexyl	0·081	0·013	13·2	32·7	44·5	58·9			+
Cyclopentyl	0·008	0·13	0·2	0·5	0·8	1·4		3·3	−
$C_6H_5CH_2$	0·362	0·007	55·5	79·9	86·8	91·9			+ +

* + + = instantaneous colouration + = faint colouration, − = no colouration.

TABLE 5. *Cis*-ENOL PERCENTAGE IN THE ENOL-FRACTION OF ETHYL α-PHENYLACETOACETATE IN DIFFERENT SOLVENTS

E	E_1	Solvent				
		CH_3COOH	$CHCl_3$	$CH_3COOC_2H_5$	C_6H_6	$C_6H_5CH_3$
4·722	0·006	98·1	98·7	99·2	99·5	99·6

The esters with branched alkyl substituents (XVI–XXII) display a far-reaching constancy in bromine consumption in different solvents and give no colour reaction with ferric chloride (see Table 4). This confirms that L' remains constant in formula (1) for *trans*-enolization of α-substituted acetoacetates and hence formula (2) may be applied in the investigation of a quantitative determination of their keto-*cis*-*trans*-enol equilibrium. This removes the doubts expressed by Eistert and Geiss[26].

In Figs. 12, 13 and 14 the dependence of K_T on Meyer's L for these substances is given. In all instances studied good linear relationships corresponding to formula (2) are observed. For compounds with branched alkyl substituents the slope of the straight lines is gradual. It increases in passing to non-branched alkyls, reaches 45° with ethyl acetoacetate (standard compound) and becomes steeper still with ethyl-α-phenylacetoacetate. The data obtained were used to calculate in terms of formula (2) the constants E and E_1 and the percentage of *cis*-enolic forms in the enol fraction of keto-enols (see Tables 4 and 5).

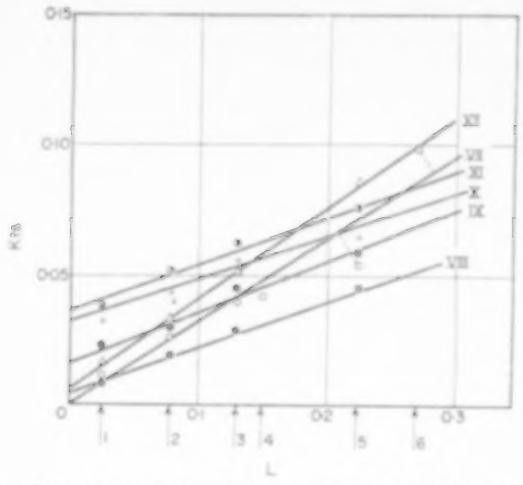


FIG. 12. Dependence of tautomeric equilibrium constant (K_T) on the solvent (constant L) for α-substituted ethylacetoacetates with non-branched substituents. $CH_3COCHRCOOC_2H_5$: VII R = CH_3, VIII R = C_2H_5, IX R = n-C_3H_7, X R = n-C_4H_9, XI R = n-C_7H_{15}, XIII R = $C_6H_5CH_2$. Solvents: (1) 67 per cent CH_3OH (2) CH_3OH (3) C_2H_5OH (4) $CH_3COOC_2H_5$ (5) C_6H_6 (6) $C_6H_5CH_3$.

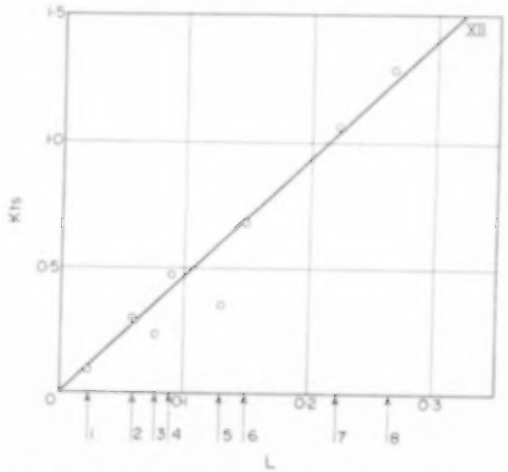


FIG. 13. Dependence of the tautomeric equilibrium constant (K_T) on the solvent (Constant L) for ethyl α-phenylacetoacetate. Solvents: (1) 67 per cent CH_3OH (2) CH_3COOH (3) CH_3OH (4) $CHCl_3$ (5) C_2H_5OH (6) $CH_3COOC_2H_5$ (7) C_6H_6 (8) $C_6H_5CH_3$

3. CONCLUSION

The solvent effect on *trans*-enolization is to a great extent dependent on the nature of the keto-enol yielding *trans*-enol, the keto-enols being classified as follows:

1. Cyclic β-diketones, such as dimedone, containing two carbonyl groups in the same ring.

These compounds have been studied in detail by Eistert *et al.* and their spectra were found to exhibit a solvent relationship not in accordance with Meyer's rule. Hydrophilic solvents show a dominance of the enolic (*trans*-) form and in hydrophobic

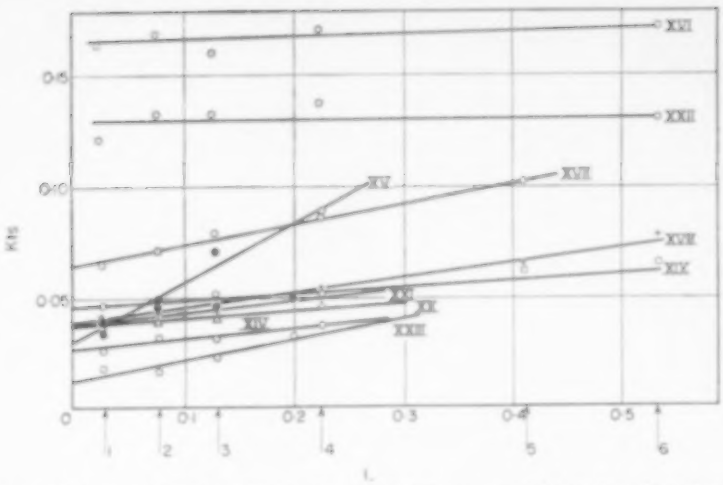


FIG. 14. Dependence of the tautomeric equilibrium constant (K_T) on the solvent (constant L) for α-substituted ethyl acetoacetates with branched substituents $CH_3CHRCOOC_2H_5$: XIV R = i-C_3H_7; XV R = i-C_4H_9; XVI R = s-C_4H_9 XVII R = 3-pentyl; XVIII R = 2-pentyl; XIX R = 2-hexyl; XX R = 2-heptyl; XXI R = 2-octyl; XXII R = cyclopentyl; XXIII R = cyclohexyl. Solvents: (1) 67 per cent CH_3OH (2) CH_3OH (3) C_2H_5OH (4) C_6H_6 (5) ether (6) CCl_4

solvents the ketonic form is present. Hence, Meyer's rule does not hold whilst the hypothesis of Eistert and Reiss is valid.

2. Cyclic β-ketolactones, such as alkyltetronic acid. The concentration of the enolic form is approximately constant in different solvents. The ethereal solvents (ether, dioxan) lead to an increased enol content, probably because in these solvents only the enolic (*trans*-) form is capable of hydrogen bonding with the ether oxygen atoms of the solvent.

In solvents containing hydroxyls, hydrogen bonds produce both ketonic (with O—H groups of the solvent) and enolic forms. Judging from the experimental results, this capacity of the two forms changes to an equal degree from one hydroxyl containing solvent to another. It is noteworthy that in dichloroethane the tautomeric equilibrium constant is the same as in water or alcohols. Neither Meyer's rule nor Eistert and Reiss' hypothesis can be applied to "*trans*-fixed" keto-enols of this type.

3. Cyclic acetals of malonic acid, such as isopropylidene alkylmalonates. Here enolization is negligible in all solvents and there is, therefore, no action of solvent on enolization. Meyer's rule and Eistert and Reiss' hypothesis do not hold.

4. Keto-enols with open chains, such as alkyl α-alkylacetoacetates. As in 2, *trans*-enolization is to a large extent independent of the solvent and ethereal solutions are characterized by a small increase in enolic forms. In the case of cyclic and non cyclic α-alkyl-β-keto-carboxylates L' may be regarded as constant in formula (1) and hence, for α-alkyltetronic acids and α-alkylacetoacetates with strong steric hindrances, EL is equal to zero and formula (1) becomes $K_T = E'L' = \text{Const}$, and (*trans*)-enolization is independent of the solvent there being virtually no *cis*-enol and the reaction with ferric chloride being negative.

For α-alkylacetoacetates with small substituents it is normal to have all three forms present in solution. It can be assumed that *trans*-enolization does not depend

on the solvent as with α-alkyltetronic acids or α-alkylacetoacetates with branched substituents, that is $L' = \text{Const}$. They differ, however, in $EL \neq 0$, formula (1) being thereby converted to formula (2). Plot $K_T = f(L)$ is a straight line with a stronger or weaker slope that cuts on the ordinate axis an intercept characteristic of *trans*-enolization. As seen from Table 4 the amount of *cis*-enolic forms increases with decreasing

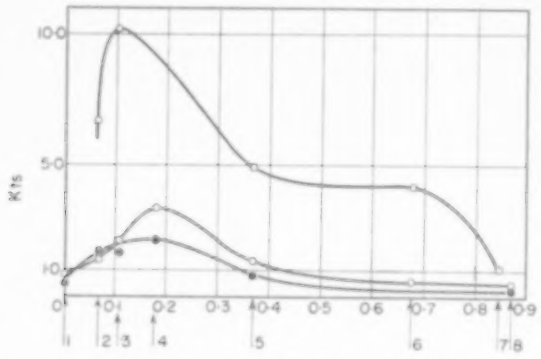


FIG. 15. Dependence of the tautomeric equilibrium constant (K_T) of cyanoketones on the solvent (constant L) with ethyl acetoacetate as standard compound.

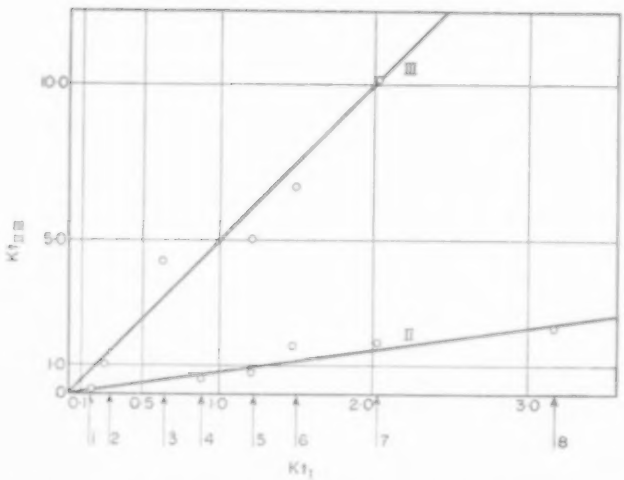


FIG. 16. Dependence of the tautomeric equilibrium constant (K_T) of cyanoketones on the solvent (constant L') with cyanodesoxybenzoin as standard compound. I-cyanodesoxybenzoin II α(2-furoyl) phenylacetonitrile; III α-(2-furoyl)-3, 4-dichlorphenyl-acetonitrile

steric hindrances caused by alkyl radicals. These compounds give a pronounced colour reaction with ferric chloride, enolization of such compounds being expressed in terms of formula (2).

5. *Enols produced from cyano-ketones studied by Russel.* In this case both the *trans*- and *cis*-enols have an open hydroxyl group and, as seen from Fig. 15 (co-ordinates K_T and L) the dependence of enolization on the solvent is very involved. The *cis*-enolizing capacity of the solvent (the Meyer's constant L) being increased, K_T passes

TABLE 6. PROPERTIES OF ETHYL α-ALKYL ACETOACETATES

Substituent R in $CH_3COCHRCOOC_2H_5$	b.p./mm	n_D^{20}	d_4^{20}	Literature data	Reference	Analyses			
						C		H	
						Found	Calc.	Found	Calc.
CH_3	66–66·5/8	1·4200	0·9989	b.p. 75–76·5°/12 mm, n_D^{15} 1·4237	32	57·8;58·0	58·3	8·4;8·6	8·3
iso-C_4H_9	105–108/16	1·4300	0·9511	b.p. 104–106°/14 mm	33	64·7;64·6	64·6	9·7;9·7	9·7
n-$C_3H_7CHCH_3$	96–99/7	1·4350	0·9492	b.p. 226°	34	66·0;66·1	66·0	10·1;10·2	10·1
$(C_2H_5)_2CH$	100/9	1·4375	0·9568	—	—	66·2;66·1	66·0	10·1;10·1	10·1
n-$C_4H_9(CH_3)CH$	118–121/10	1·4370	0·9433	b.p. 130–132°/17 mm	35	67·2;67·2	67·2	10·4;10·3	10·3
n-$C_5H_{11}(CH_3)CH$	123–124/8	1·4388	0·9331	b.p. 250–260°	36	68·7;68·6	68·5	10·8;10·4	10·6
s-C_4H_9	68/3	1·4350	0·9584	b.p. 102/104°/15 mm	37	64·5;64·6	64·5	9·8;9·8	9·7
n-$C_6H_{13}(CH_3)$ CH	114–116/2	1·4397	0·9254	b.p. 280–282°	38	69·6;69·7	69·4	11·0;11·1	10·8
n-C_7H_{15}	122–124/3	1·4365	0·9291	b.p. 141·6/10 mm n_D^{15} 1·4376 d_4^{15} 0·9327	39	68·1;68·2	68·5	10·5;10·5	10·6
Cyclopentyl	115/7	1·4570	1·0155	b.p. 118–120°/12 mm; n_D^{20} 1·4646	40	66·7;67·0	66·6	9·1;9·3	9·2
Cyclohexyl*	95–96/3	1·4618	1·0386	b.p. 146–148°/12 mm	41	67·9;67·6	67·9	9·3;9·3	9·5
C_6H_5†	113–115/2·5	1·5170	1·0855	b.p. 130–134°/5 mm	42	69·9;70·0	69·9	6·8;6·9	6·8
$C_6H_5CH_2$	110·5–112/2	1·5056	1·0636	b.p. 164–165°/12 mm	43	70·6;70·4	70·9	7·3;7·3	7·3

* Obtained from ethyl acetoacetate, cyclohexanol, and BF_3

† Obtained via α-phenyl-α-acetylacetonitrile

[32] J. W. Bruhl, *J. Prakt. Chem.* (2) **50,** 128 (1894).
[33] G. Tafel, *Ber. Dtsch. Chem. Ges.* **42,** 2555 (1909).
[34] L. Clarke, *Ber. Dtsch. Chem. Ges.* **40,** 353 (1907).
[35] F. H. Less, *J. Chem. Soc.* **81,** 1594 (1902),
[36] F. P. Venable, *Ber. Dtsch. Chem. Ges.* **13,** 1651 (1880).
[37] G. Tafel, *Ber Dtsch. Chem. Ges.* **45,** 449 (1912).
[38] M. Guthzeit, *Liebigs Ann.* **204,** 2 (1880).
[39] P. Centerick, *Bull. Soc. Chim. Belg.* **45,** 545 (1936).
[40] K. Burschkies and G. School, *Arch. Pharm.* **281,** 328 (1943).
[41] G. T. Adams, B. Abramovitch and C. R. Hauser, *J. Amer. Chem. Soc.* **65,** 552 (1943).
[42] *Organic Syntheses* Vol. 18, p. 36.
[43] H. Lenchs, *Ber. Dtsch. Chem. Ges.* **44,** 510 (1911).

through the maximum. These curves become straight lines when applying L' (formula 1) instead of L, that is when substituting the standard compound. If any cyano-ketone is taken as standard, good linear relationships are observed and the straight lines pass through the origin (Fig. 16). Enolization to form a chelated enol being impossible in this case, $E = 0$ and formula (1) becomes similar to that of Meyer, $K_T = E'L'$ but differing from it as to the standard compound. Here again the relatively high enolizing capacity of ether may be due to its hydrogen bonding with the open hydroxyl group of the enolic form. Thus for this case both Meyer's rule and Eistert and Reiss' hypothesis do not hold true but when choosing a suitable standard compound formula $K_T = E'L'$ can be applied.

The above types of keto-enols do not exhaust all the possibilities of solvent effect on *trans*-enolization and even these examples point to the great variety of such effects; only types such as dimedon follow the hypothesis suggested by Eistert and Reiss.

Formula (1) is of a general character and its application depends on the right choice of standards for L and L'. Formula (2) is of a more limited value and can be applied only to those systems characterized by $L' = \text{Const}$.

EXPERIMENTAL

The α-substituted acetoacetates were produced by alkylating sodium ethyl acetoacetate with suitable alkyl halides, the properties of the compounds investigated are listed in Table 6.

Isopropyliden ethylmalonate m.p. 107° was obtained as described previously.[14] (Found: C, 56·1, 56·1; H, 7·2, 7·3. Calc. for $C_9H_{12}O_4$: C, 55·8; H, 7·0%).

Deuterated isopropylidene ethylmalonate, m.p. 107°. (Found: C, 55·4, 55·2; H, 7·0, 7·0. Calc. for $C_9H_{11}OD$: C, 55·5; H, 7·6%).

Ethyltetronic acid, m.p. 127–128° and propyltetronic acid, m.p. 126° were obtained as described.[43]

Lactone of γ-hydroxy-α,α-dimethylacetoacetic acid was synthesized according to Conrad[46] from ethyl γ-acetoxy-α,α-dimethylacetoacetate, b.p. 72·5°/5 mm; n_D^{20} 1·4483; d_4^{20} 1·1496. (Lit. b.p. 208–209°; d_{15}^{15} 1·147. (Found: C, 56·2, 56·3; H, 6·6, 6·6. Calc. for $C_6H_8O_3$: C, 56·2; H, 6·3%.)

The bromometrical titration of 1 per cent solutions was carried out according to Hesse and Krehbiel with alcoholic bromine solution.

The pH determination of solutions for spectral study was carried out with a potentiometer LP-5 with an accuracy of 0·05 pH units.

The infra-red spectra were obtained on a double beam spectrometer IKS-14. The samples of crystalline compounds were pressed together with potassium bromide.

The ultra-violet spectra were taken on spectrometer SFD-1. The concentration of solutions investigated is referred to in the text in subtitles.

[45] P. Ott, *Liebigs Ann.* **401**, 159 (1913).
[45] M. E. Demarcay, *Bull. Soc. Chim.* (2) **27**, 484 (1878).
[46] M. Conrad and R. Gast, *Ber. Dtsch. Chem. Ges.* **31**, 2726 (1898).
[47] C. F. Koelsch, *J. Amer. Chem. Soc.* **60**, 306 (1944).

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THE STEREOCHEMISTRY OF SOME HALOGENOCHOLESTAN-3-ONES

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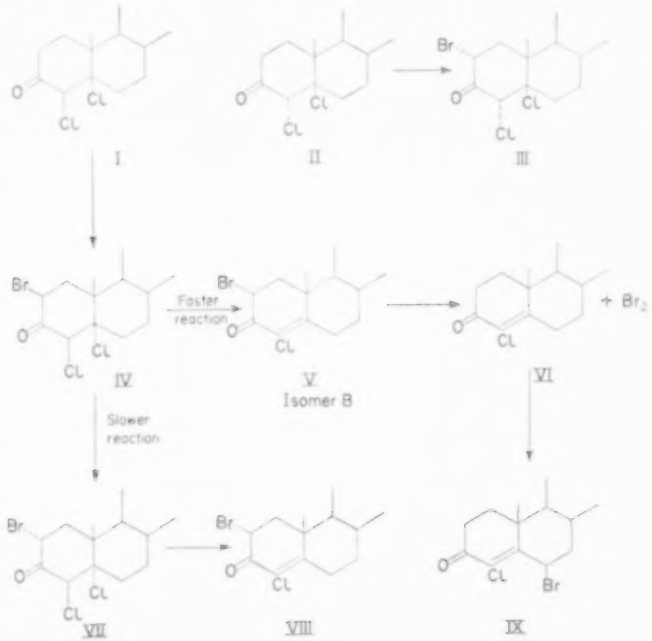
(*Received* 30 *August* 1960)

Abstract—The stereochemistry of the 4,5-dichloro- and 2-bromo-4,5-dichloro-derivatives[1] of cholestan-3-one is discussed.

THE present communication completes earlier studies[1] on 4,5-dichloro-cholestan-3-one by establishing its stereochemistry.

Information on the orientation of a halogen atom (other than fluorine) in an α-halogeno steroidal 3-ketone may generally be obtained:

(i) From the infra-red spectrum. The carbonyl stretching band found in the region 1719–1713 cm^{-1} is displaced by about +16 to +21 cm^{-1} by an equatorial halogen atom, but is hardly affected by an axial halogen atom.[2]



(ii) From the low intensity U.V. absorption band (R-band) at 280–286 mμ characteristic of an unsubstituted 3-oxo steroid. This band is displaced to a longer

[1] D. N. Kirk, D. K. Patel and V. Petrow, *J. Chem. Soc.* 1184 (1956); D. N. Kirk and V. Petrow, *Ibid.* 1334 (1958).
[2] R. N. Jones and F. Herling, *J. Org. Chem.* **19**, 1252 (1954); R. N. Jones, D. A. Ramsey, F. Herling and K. Dobriner *J. Amer. Chem. Soc.* **74**, 2828 (1952).

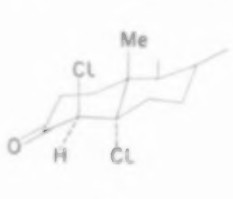
wavelength by an axial halogen atom with a concomitant marked increase in the extinction coefficient. An equatorial halogen substituent, in contrast, causes only a very small hypsochromic shift of the absorption maximum.[3]

(iii) By reduction with an alkali metal borohydride followed by treatment of the resulting halohydrin with alkali. *Trans*-halohydrins yield epoxides under these conditions, whilst *cis*-halohydrins afford ketones. Catalytic dehalogenation of the halohydrin will generally give an alcohol of known configuration, thereby permitting the stereochemistry of the halohydrin, and thence of the haloketone, to be established.[4]

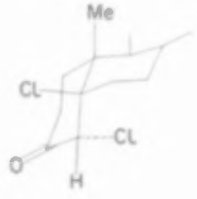
In attempting to determine the stereochemistry of 4,5-dichloro-cholestan-3-one, we turned initially to chemical procedure (iii) above. Reduction of the dihaloketone with lithium borohydride in tetrahydrofuran afforded an apparently homogeneous dichloroalcohol, which was characterized as an acetate. Reaction of the dichloroalcohol with alkali, however, failed to give indication of its structure. Thus, it was recovered unchanged after heating with 2 per cent ethanolic potassium hydroxide, whilst 20 per cent ethanolic potassium hydroxide converted it into an intractable black tar. Attention was therefore directed to physical methods.

The ultra-violet absorption of 4,5-dichlorocholestan-3-one reaches a maximum at 301 mμ, indicating an axial conformation for the 4-chloro substituent.[3] Examination of models, however, reveals the possible existence of two 4-axially substituted structures, namely 4β,4α-dichloro-cholestan-3-one (I) and 4α,5β-dichloro-5β-cholestan-3-one (II). These structures both conform to the rule of diaxial addition[5] of halogen to an ethylenic linkage. Alternative structures involving a boat-shaped Ring A may be rejected as they cannot be formed by the energetically preferred *trans*-diaxial addition of chlorine to cholest-4-en-3-one, and moreover would be destabilized by the proximity of the halogen atoms.

Bromination of 4,5-dichlorocholestan-3-one[1] (I or II) furnished a mono-substitution



I



II

product (m.p. 110–111°) formulated as a 2ξ-bromo-4,5-dichlorocholestan-3-one.[1] Its U.V. absorption spectrum showed that introduction of the bromine atom at C_2 had been accompanied by a bathochromic shift of 25 mμ in the absorption maximum, thereby indicating an axial conformation for the newly introduced halogen atom.[3] The constitution of 2β-bromo-4β,5α-dichlorocholestan-3-one (IV), derived from structure I, was indicated for this product. At the same time the alternative 2α,4α-diaxial structure (III) could not be excluded from consideration at this stage. It is true that 3-keto-5β-steroids generally brominate at C_4. In this case, however, (i) the

[3] R. C. Cookson, *J. Chem. Soc.* 282 (1954).
[4] J. J. Beereboom and C. Djerassi, *J. Org. Chem.* **19**, 1196 (1954); L. F. Fieser and R. Ettore, *J. Amer. Chem. Soc.* **75**, 1700 (1953); L. F. Fieser and X. A. Dominguez, *Ibid* **75**, 1704 (1953); E. J. Corey, *Ibid.* **75**, 4832 (1953); L. F. Fieser and W-Y Huang, *Ibid.* **75**, 4837 (1953).
[5] D. H. R. Barton and E. Miller, *J. Amer. Chem. Soc.* **72**, 370 (1950); G. H. Alt and D. H. R. Barton, *J. Chem. Soc.* 4284 (1954).

inductive effect of the 4-chloro-substituent would reduce the tendency of the 3-keto group to enolize towards C_4, and (ii) the preference for the participation of an axial hydrogen atom in the enolization of a cyclic ketone, demonstrated by Corey[6] and attributed by him to a stereoelectronic effect, would also tend to favour enolization and subsequent bromination at C_2 in the 4α-chloro ketone (II) in which the 4β-hydrogen atom has the unfavourable 4β (equatorial) conformation. A decision in favour of structure IV was ultimately reached as indicated below.

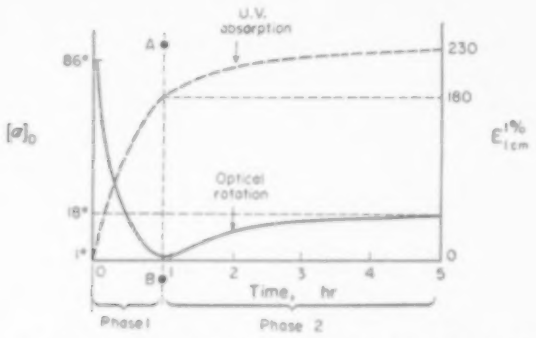


FIG. 1. Reaction between 2β-bromo-4β,5α-dichlorocholestan-3-one (of $[\alpha]_D + 86°$) and pyridine (1% each) in chloroform (Points A and B represent the optical rotation of the pure products, isomers A and B, respectively).

TABLE 1. CHANGES OF ULTRA-VIOLET ABSORPTION IN THE DEHYDROCHLORINATION OF 2β-BROMO-4β,5α-DICHLOROCHOLESTAN-3-ONE WITH 1% PYRIDINE IN CHLOROFORM

Time (hours)	0·0	0·20	0·50	0·83	1·33	3·00	24
λ_{max} (mμ)	—	267	267	267	266	265	264·5
$E^{1\%}_{1\,cm}$ at λ_{max}	—	101	152	170	192	225	230

We had previously shown[1] that dehydrochlorination of the 2ξ-bromo-4,5-dichlorocholestan-3-one (III or IV) leads in modest yield to the formation of a 2ξ-bromo-4-chlorocholest-4-en-3-one, m.p. 183°, $[\alpha]_D$ +90° (*Isomer* A). The optical rotatory and U.V. changes occurring during its formation from the 2ξ-bromo-4,5-dichlorocholestan-3-one in a 1 per cent pyridine/chloroform solution, however, appeared to indicate the concomitant formation of a second product with a lower optical rotation and an absorption maximum at a longer wavelength (Fig. 1 and Table 1). Search for this product led to the isolation of an isomeric 2ξ-bromo-4-chlorocholest-4-en-3-one, m.p. 115°, $[\alpha]_D$ −3° (*Isomer* B). Both isomers passed into 4-chlorocholesta-1,4-dien-3-one[1] on dehydrobromination with lithium chloride/dimethyl formamide. Comparison of their ultra-violet absorption spectra (Table 2) established unequivocally the constitution of the new *Isomer* B as the 2β-(quasi axial) epimer V and that of the previously known *Isomer* A as the 2α-(quasi equatorial) epimer VIII.

The bathochromic shifts and enhancement of extinction coefficients of the peaks in the R bands of the 2β (axial) bromo-derivative are similar to those reported by

[6] E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.* **78**, 6269 (1956).

Cookson[7] for 6β *axial*-bromo-Δ^4-3-keto steroids. Cookson's explanation of this effect in terms of overlap of the σ-bonding electron orbital, or of the p-electrons of the bromine atom, with the conjugated π-orbital system of the unsaturated ketone in the axial epimer, can be assumed to apply also to the 2-bromo-derivative. The relative positions and intensities of the K-bands support the configurations assigned to these bromo-compounds.

Following the isolation of 2β-bromo-4-chlorocholest-4-en-3-one (V) attempts

TABLE 2. PROPERTIES OF 2α- AND 2β-BROMO-4-CHLOROCHOLESTENONES

			K-band		
	M.p.	$[\alpha]_D$	λ_{max}	ε_{max}	
4-Chlorocholestenone	126–7°	+106°	256 mμ	14,110	
2α-Bromo-4-chlorocholestenone	181–3°	+90°	260 mμ	10,200	
2β-Bromo-4-chlorocholestenone	113–5°	−3°	267 mμ	11,330	
	U.V.-absorption (R-band)				
4-Chlorocholestenone	313(40[a])	324(41)	337(33)	350(19)	368(6)
2α-Bromo-4-chlorocholestenone	314(54)	326[b](45)	344[b](28)	356[b](15)	366[b](8)
2β-Bromo-4-chlorocholestenone	335(115)	346(99)	—	366(53)	374(26)

[a] Values in parentheses are extinction coefficients (ε).
[b] Inflexion.

were made to epimerize it into the 2α-*quasi-equatorial*-bromo isomer (VIII) by treatment with pyridine. Its solution in this solvent, however, failed to undergo change in optical rotation after 8 hours at room temperature. Further treatment with pyridine led to its conversion after several days into an acid-soluble product, which was probably a pyridinium compound and was not investigated further. The 2α-isomer (VIII) showed even greater stability to pyridine treatment. It was consequently mandatory to draw the unexpected conclusion that formation of *Isomer* A from 2ξ-bromo-4,5-dichlorocholestan-3-one (III or IV) does not occur through epimerization of *Isomer* B.

It was possible at this stage to interpret the reactions responsible for the optical rotatory changes given in Fig. 1. The equilibrium optical rotation of +10° recorded in Fig. 1 implies that the 2α-(*Isomer* A) and 2β-bromo (*Isomer* B)-epimers are present in the ratio 1:3 (approx). Figure 1 additionally reveals the significant fact that the first stage of the reaction (complete after ca. 1 hour) is characterized by a rapid fall in optical rotation to a value (+1°) corresponding approximately to that of *Isomer* B (−3°). At this point the ultra-violet absorption of the mixture (cf. Table 1) in the $\alpha\beta$-unsaturated ketone region also corresponds to that of *Isomer* B with only minimal quantities of *Isomer* A being present. Thereafter prolongation of the reaction leads to an increase in optical rotation and a shift in the absorption maximum to shorter wavelengths owing to the gradual appearance of *Isomer* A, which represents the minor product of the reaction and which, as shown above, is not formed from *Isomer* B by isomerization.

[7] C. W. Bird, R. C. Cookson and S. H. Dandegaonker, *J. Chem. Soc.* 3675 (1956).

These changes unequivocally exclude structure III for the 2ξ-bromo-dichlorocholestan-3-one. Conversion of III into *Isomer* B would involve inversion of the bromine atom at C_2, followed by dehydrochlorination. As *Isomer* B forms the major product, these two reactions would necessarily proceed at a faster rate than the simple dehydrochlorination of the bromo-dichloro compound (III) into *Isomer* A. If this were indeed the case, then the accumulation of *Isomer* A in the solution after *Isomer* B had reached maximal concentration simply could not occur. Formula III consequently

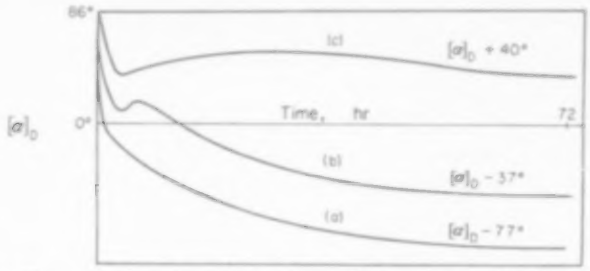


FIG. 2. Changes in optical rotation with time during reaction of 2β-bromo-4β,5α-dichlorocholestan-3-one (IV) with HBr/acetic acid in the presence of (a) no β-naphthol, (b) 1 mole β-naphthol, (c) 5 moles β-naphthol.

fails to accommodate the observed facts. The changes revealed by Fig. 1 are, however, readily explained on the basis of structure IV for the 2ξ-bromo-4,5-dichlorocholestan-3-one. The last compound may be regarded as undergoing simultaneously two competing reactions. The faster reaction involves simple dehydrochlorination to *Isomer* B. The somewhat slower reaction involves the epimerization of the 2β-bromo-substituent to the 2α-conformation to give 2α-bromo-4β,5α-dichlorocholestan-3-one (subsequently prepared from IV by treatment with hydrochloric acid/acetic acid *vide infra*), which then undergoes dehydrochlorination. The end of the first phase of the reaction of IV with pyridine (Fig. 1) consequently represents conversion of the starting material into V and VII. Subsequently, VII undergoes dehydrochlorination into *Isomer* A which accumulates in the solution *after maximum concentration of* Isomer B *has been reached.*

After completion of this investigation towards the middle of 1957 Professor C. Djerassi kindly examined the optical rotatory dispersion of the 4,5-dichloro-ketone (I), and confirmed the 4β,5α-configuration. This conclusion depends upon the observed negative Cotton effect in the O.R.D. curve for the compound, which suggests that the axial chlorine atom at C-4 has the β-configuration.[8]

Attempts to invert the 2β-bromo substituent of the bromo-dichloro-compound (IV) with hydrobromic acid in acetic acid led to the formation of 6β-bromo-4-chlorocholest-4-en-3-one[1] (IX). The optical rotatory changes accompanying this conversion are shown in Fig. 2 (curve a). They indicate initial rapid dehydrochlorination to 2β-bromo-4-chlorocholest-4-en-3-one (V), followed by slow migration of the bromine atom to C_6. That the latter reaction involves removal of the bromine atom at C_2 with transitory formation of molecular bromine, followed by bromination at C_6, was shown by interception of the molecular bromine with β-naphthol. This procedure had been

[8] C. Djerassi and W. Klyne, *J. Amer. Chem. Soc.* **79**, 1506 (1957); C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *Ibid.* **80**, 1216 (1958).

used by Crowne *et al.*[9] to demonstrate the participation of molecular bromine in the hydrogen bromide catalysed conversion of 2,2-dibromo- into 2α,4α-dibromocholestan-3-one. In the present case the competing reaction between the steroid and the bromine could not be wholly eliminated, even in the presence of a 5-fold excess of β-naphthol, although in this instance the main steroidal product was 4-chlorocholest-4-en-3-one (VI).

The elimination of hydrogen chloride from 2β-bromo-4β,5α-dichlorocholestan-3-one (IV) under the influence of hydrogen bromide/acetic acid to give 2β-bromo-4-chlorocholest-4-en-3-one (V, above) requires the presence of bromide ion (Br^-) and is not a general acid-catalysed process. Thus when sulphuric or toluene *p*-sulphonic acid was substituted for hydrogen bromide (all at 0·16 N), no change in optical rotation was observed after 24 hours at room temperature. When hydrogen chloride (10% w/w) or perchloric acid (2·5 N) in acetic acid were used, in contrast, the optical rotation of the solution fell from $[\alpha]_D$ +86° to $[\alpha]_D$ − 1° after 24 hours, and remained constant thereafter. The product so formed was an amorphous solid which resisted crystallization. Its spectroscopic examination revealed a 3 per cent content of αβ-unsaturated ketonic material ($\varepsilon_{261\cdot5}$ 315). Analyses showed virtually no loss of halogen. Reaction with pyridine at room temperature gave an almost quantitative yield of 2α-bromo-4-chlorocholest-4-en-3-one (VIII). The new product is accordingly formulated as 2α-bromo-4β,5α-dichlorocholestan-3-one (VII) and results from acid-catalysed inversion of the 2β-bromo substituent of IV. It represents the essential intermediate in the chain of reactions leading from IV to Isomer A (VIII) *vide supra*.

It seemed likely that the difference in behaviour of 2β-bromo-4β,5α-dichlorocholestan-3-one (IV) towards hydrobromic and hydrochloric acid/acetic acid stemmed from the greater nucleophilic reactivity of the bromide ion relative to the chloride ion. The bromide ion, acting as a base, was envisaged as abstracting a proton from the C_4 position of IV with subsequent loss of chloride ion from C_5. In order to test this hypothesis, the substitution of bromide ion by the even more nucleophilic iodide ion was examined.

Initially, a solution of hydrogen iodide in acetic acid was added to a solution of the 2β-bromo-compound (IV) dissolved in chloroform. Instantaneous reaction occurred with liberation of iodine, rendering polarimetric determinations impossible. By using the bromine-free 4β,5α-dichlorocholestan-3-one (I), however, it proved possible to examine the effect of the three halogen ions upon the analogous dehydrochlorination reaction leading to 4-chlorocholest-4-en-3-one (VI).

A one per cent solution of 4β,5α-dichlorocholestan-3-one (I) in 10 per cent of hydrogen chloride (w/w) in acetic acid/chloroform (9:1) was found to undergo change in optical rotation from $[\alpha]_D$ + 5° to $[\alpha]_D$ +96°, with a half-life period of 162 minutes to give 4-chlorocholest-4-en-3-one (VI). By using such a solution and adding to it the halide ion under examination in the form of its lithium salt, it proved possible to compare the accelerating effects of the three halide ions upon the dehydrochlorination of the dichloro-compound (I) under equivalent conditions. The results obtained (Table 3 and Fig. 3) reveal the expected order of nucleophilic reactivity for the three halide ions, with $Cl^- < Br^- < I^-$.

A somewhat different situation obtains with 2β-bromo-4β,5α-dichlorocholestan-3-one (IV). Under acidic catalysis the 3-keto group enolizes almost exclusively in the

[9] C. W. P. Crowne, R. M. Evans, G. F. H. Green and A. G. Long, *J. Chem. Soc.* 4351 (1956).

direction of C_2 *vide supra* with consequent inversion of the 2β-bromo substituent to the more stable 2α-configuration (i.e. to VII). Further reaction leading to dehydrochlorination does not occur with chloride ion, for example, which does not possess sufficient nucleophilic reactivity to enforce extrusion of a proton from C_4. In the presence of the more nucleophilic bromide ion, in contrast, the base-catalysed dehydrochlorination reaction occurs at an appreciable rate, and this reaction becomes dominant when a relatively strong base such as pyridine is employed.

TABLE 3. HALF-REACTION TIMES FOR THE DEHYDROCHLORINATION OF 4β,5α-DICHLOROCHOLESTAN-3-ONE BY HYDROGEN CHLORIDE/LITHIUM HALIDE IN ACETIC ACID/CHLOROFORM

Reagent	Concentration of lithium halide	Half-reaction time (min)
(a) 10% HCl	—	162
(b) 10% HCl + LiCl	1·0 N	84
(c) 10% HCl + LiBr	1·0 N	12
(d) 10% HCl + LiBr	0·25 N	65
(e) 10% HCl + LiI*	0·25 N	36

* LiI could not be employed at 1·0 N concentration owing to the rapid appearance in the solution of free iodine. This prevented the measurement of $[\alpha]_D$ within a few minutes.

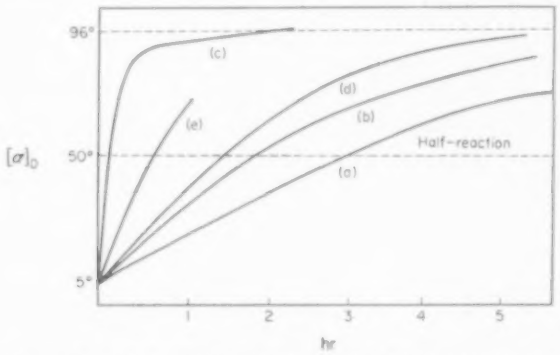


FIG. 3. Changes in optical rotation with time during dehydrochlorination of 4β,5α-dichlorocholestan-3-one by HCl in the presence of lithium halide. (a) No Li halide. (b) 1·0 N LiCl. (c) 1·0 N LiBr. (d) 0·25 N LiBr. (e) 0·25 N LiI.

The observation that 'acidic' (electrophilic) attack involves C_2, whilst 'basic' (nucleophilic) attack involves C_4 preferentially may be rationalized in terms of two distinct controlling factors. It is known that enolization of 3-oxo-5α-steroids leads to appearance of a double bond at C_2—C_3.[10] This has been attributed to hyperconjugation, the Δ^2-linkage being stabilized by one more hydrogen atom than obtains for a C_3—C_4 double bond. This essentially thermodynamic control may be expected to operate in the acid catalysed enolization of IV. Base-catalysed enolization, however,

[10] D. A. H. Taylor, *Chem. & Ind.* 250 (1954); A. S. Dreiding, *Ibid.* 1419 (1954).

is probably kinetically controlled. The C_4 hydrogen atom is more acidic in character than the one at C_2 owing to the greater polarization of the C—Cl bond compared to the C—Br bond.[11] Attack by base accordingly takes place preferentially, but not exclusively at C_4.

Yet a further effect demands recognition. Kinetic control of the rate-controlling step, viz. removal of a proton from C_4, would presumably apply in equal measure to both the 2-bromo epimers IV and VII. If this were indeed the case, then the rates of dehydrochlorination of these two isomers IV and VII would be expected to be similar.

It has been shown above that the first part of the curve in Fig. 1, representing the change in optical rotation with time in the reaction of the 2β-bromo-dichloride (IV) with pyridine corresponds approximately to the dehydrochlorination step (IV) → (V). The half-life of the 2β-bromo-dichloride (IV) estimated from this part of the curve is approximately 7 minutes. The half-life of the 2α-bromo isomer (VII) under similar conditions, however, is found to be ca. 42 minutes.

These results point to the existence of yet another rate-controlling factor which is believed to stem from stereoelectronic control associated with the centre at C_2. As already mentioned, Corey[6] has shown that enolization of cyclic ketones preferentially occurs through removal of an axial hydrogen atom. Such an axial hydrogen atom is present (at C_2) in the 2α-bromo-epimer (VII) but not in the 2β-bromo-compound (IV). Enolization towards C_4 will consequently be less marked in VII than in IV. But enolization towards C_4 is regarded as the rate-controlling step in the dehydrochlorination reaction leading to the introduction of the Δ^4-linkage. Dehydrohalogenation should consequently occur more readily in IV than in VII, which is indeed found to be the case.

The foregoing kinetic experiments were carried out under ordinary laboratory conditions, and not under strictly physico-chemical temperature control etc. The significance of the results must therefore be regarded as qualitative rather than accurately quantitative.

EXPERIMENTAL

Optical rotations were measured in $CHCl_3$ solutions in a 1 dm tube, unless otherwise stated. Ultra-violet and infra-red absorption spectra were kindly determined by Mr. M. T. Davies, B.Sc.

Reduction of 4β,5α-dichlorocholestan-3-one with lithium borohydride

4β 5α-Dichlorocholestan-3-one (2 g) in purified tetrahydrofuran (40 ml) was added to lithium borohydride (1 g) in tetrahydrofuran (40 ml) and the mixture stirred for 4 hr at room temp, when it was poured into water. The product was isolated with ether and purified from ethanol giving *4β,5α-dichlorocholestan-3ξ-ol* in fine needles, m.p. 163–164°, $[\alpha]_D^{24}$ +18° (*c*, 0·20). (Found: C, 71·4; H, 10·4; Cl, 15·6. $C_{27}H_{46}OCl_2$ requires: C, 70·9; H, 10·1; Cl, 15·5%).

The *3-acetate* prepared by acetylation with acetic anhydride and pyridine on the steambath for 45 min followed by purification from ethanol formed flakes, m.p. 100–101°, $[\alpha]_D^{16}$ +1° (*c*, 0·24). (Found: C, 69·6; H, 9·7; Cl, 14·3. $C_{29}H_{48}O_2Cl_2$ requires: C, 69·7; H, 9·7; Cl, 14·2%).

Polarimetric experiments. The general procedure was as follows: The steroid was weighed into a stoppered flask, dissolved in the appropriate volume of solvent (chloroform, etc.), and treated with the required volume of reagent (hydrogen bromide solution, pyridine, etc.). After shaking, a 1 dm polarimeter tube was filled and placed in the polarimeter, and readings were taken as soon as practicable, usually within 2–5 minutes after mixing, although the first sets of readings were somewhat erratic due to striations in the solutions. The mean of 10 readings was taken as the optical rotation at the time noted after the fifth reading for each set.

[11] C. K. Ingold, *Structure and Mechanism in Organic Chemistry* p. 446. G. Bell and Sons, London (1953).

Reaction of 2β-bromo-4β,5α-dichlorocholestan-3-one with pyridine

A solution of the bromodichlorocompound (1 g) in "Analar" chloroform (99 ml) was treated with pyridine (1 ml). The optical rotatory changes of a portion of the solution were observed as above. From the main bulk of the solution 5 ml portions were withdrawn at intervals, and added to an excess of dil sulphuric acid. The chloroform was washed neutral, the washings being re-extracted with chloroform. The solvent was removed *in vacuo* at 40°, and the ultra-violet absorption of the residue determined in ethanol solution. The results are recorded in Fig. 1 and Table 1.

From a similarly-composed reaction mixture the following products were isolated after 5 hr by fractional crystallization from ethanol: 2α-bromo-4-chlorocholest-4-en-3-one (195 mg), m.p. 178–180°, λ_{max} 260 mμ (ε = 10,200) in ethanol, and *2β-bromo-4-chlorocholest-4-en-3-one* (150 mg), leaflets, m.p. 113–115°, $[\alpha]_D^{25}$ −3° (*c*, 0·37), λ_{max} 267 mμ (ε = 11,330) in ethanol, R-band: see Table 2. (Found: C, 64·8; H, 8·4; Hal., 22·6. $C_{27}H_{42}OClBr$ requires: C, 65·1; H, 8·5; Hal., 23·2%).

Dehydrobromination of 2β-bromo-4-chlorocholest-4-en-3-one

The 2β-bromo compound (300 mg) and lithium chloride (30 mg) in dimethylformamide (5 ml) were heated under reflux for 30 min, then cooled and diluted with water to turbidity. The separated solids (m.p. 118–120°) were purified from aqueous methanol to give 4-chlorocholesta-1,4-dien-3-one, needles, m.p. 128–129°, identified by comparison with an authentic sample.

Reaction of 2β-bromo-4β,5α-dichlorocholestan-3-one with hydrogen bromide

A solution of the bromodichloro-compound (1 g) in methylene chloride (5 ml) was mixed with hydrogen bromide in acetic acid (45 ml of 0·18 N soln.). The optical rotation of the mixture was followed until it became constant after 72 hr (Fig. 2a). The methylene chloride was then removed under reduced pressure and the residual acetic acid solution diluted to turbidity. The solids which separated were purified from methanol to give 6β-bromo-4-chlorocholest-4-en-3-one, m.p. 168–170°, identified by comparison with an authentic sample and by its conversion into 4-chlorocholesta-4,6-dien-3-one, needles, m.p. 97–99°.

Reaction in the presence of β-naphthol. The foregoing reaction was repeated, with the preliminary addition of β-naphthol to the hydrogen bromide/acetic acid solution. Two experiments were performed employing 0·5 g of steroid, and 150 mg (1·1 moles) or 750 mg (5·5 moles) of β-naphthol, respectively, with the results recorded in Fig. 2 (b and c), and the related discussion.

Isomerization of 2β-bromo-4β,5α-dichlorocholestan-3-one with hydrogen chloride

The bromodichloro-compound (2 g) in methylene chloride (10 ml) was mixed with 11% (w/w) hydrogen chloride/acetic acid (90 ml). The optical rotation of the solution fell from $[\alpha]_D$ +86° to $[\alpha]_D$ −1° after 24 hr, when more methylene chloride was added, and the solution washed neutral. The solvent was removed under reduced press. The residual gum, which could not be crystallized, had λ_{max} 261–265 mμ (ε = 315), indicating ca. 3% of αβ-unsaturated ketonic material.

In a second experiment, omitting the methylene chloride, the acetic acid solution was poured, after 2 days at room temp, into ice-water, and the solids collected and dried. The product, consisting essentially of *2α-bromo-4β,5α-dichlorocholestan-3-one*, had m.p. 30–50°, $[\alpha]_D^{24}$ −2° (*c*. 0·26), R-band: No U.V. absorption maximum between 260 and 340 mμ in cyclohexane. (Found: C, 61·3; H, 8·1; Hal, 26·6. $C_{27}H_{42}OCl_2Br$ requires: C, 60·7; H 8·1; Hal., 28·2%).

Dehydrochlorination of 2α-Bromo-4β,5α-dichlorocholestan-3-one with pyridine

A solution of the foregoing 2α-bromo-dichloro-compound (0·5 g) in chloroform (49·5 ml) was mixed with pyridine (0·5 ml). The optical rotation of the solution changed from $[\alpha]_D$ −3° to $[\alpha]_D$ +74° after 6 hr, with a half-reaction time of 42 min. The solution was washed with dil sulphuric acid and water, dried and the solvent evaporated. Purification from ethanol gave 2α-bromo-4-chlorocholest-4-en-3-one, m.p. 178–180°, not depressed in admixture with an authentic sample.

Dehydrochlorination of 4β,5α-dichlorocholestan-3-one in the presence of hydrogen ions and halide ions

(1) *Chloride ions.* Anhydrous lithium chloride (1·06 g) in 11% (w/w) hydrogen chloride/acetic acid solution (22·5 ml) was mixed with a solution of 4β,5α-dichlorocholestan-3-one (250 mg) in

chloroform (2·5 ml), the final concentration of lithium chloride being 1·0 N. After 24 hr 4-chlorocholest-4-en-3-one was isolated.

(2) *Bromide ions*. (a) Lithium bromide (2·18 g, to give a 1·0 N soln.) was substituted for lithium chloride in (1). (b) Lithium bromide (0·55 g; 0·25 N soln.) was used as above.

(3) *Iodide ions*. Lithium iodide (0·875 g, to give a 0·25 N soln.) was substituted for lithium chloride in (1). In this case iodine was liberated slowly into the solution, but it proved possible to observe the optical rotation at intervals up to 38 min ($[\alpha]_D$ +52°). The half-reaction time was 36 min ($[\alpha]_D$ +50°).

The results are recorded in Fig. 3 and Table 3. All the above reactions gave 4-chlorocholest-4-en-3-one in high yield.

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STRUCTURE AND STEREOCHEMISTRY OF JATAMANSONE*

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(*Received* 11 *August* 1960)

Abstract—On the basis of degradation studies, jatamansone is shown to have the structure and stereochemistry depicted in formula I, representing a new fundamental type.

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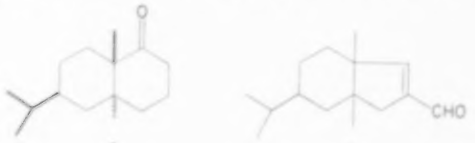
THE isolation of a sesquiterpene ketone, jatamansone from *Nardostachys jatamansi* was reported earlier.[1] On the basis of degradation studies reported in the present communication, jatamansone can unequivocally be assigned the structure and stereochemistry depicted in formula I.

Analytical results on jatamansone, its derivatives and all the degradation products are consistent with the formulation of jatamansone as $C_{15}H_{26}O$. Wolff–Kishner reduction of jatamansone yields the saturated hydrocarbon, jatamansane, $C_{15}H_{28}$ Jatamansone should therefore be a bicyclic saturated ketone.

Jatamansone was reduced by lithium aluminium hydride to jatamansol, which on dehydration with PBr_3–aniline yields jatamansene, $C_{15}H_{26}$. Ozonolysis of jatamansene yields a dialdehyde, $C_{15}H_{26}O_2$, which is converted by refluxing with alcoholic hydrochloric acid to an α,β-unsaturated aldehyde, $C_{15}H_{24}O$, (II) yielding a red 2,4-dinitrophenylhydrazone, obtained also directly from the dialdehyde. With excess benzaldehyde, both under acid as well as base-catalysed conditions, the same monobenzylidene



I II

derivative is formed, from which it may be concluded that there is no change in the carbon skeleton of jatamansone during this process. Ozonolysis of the benzylidene derivative yields jatamansic acid, also obtained[1] directly by the chromic acid oxidation of jatamansone.

Jatamansone shows infra-red absorption at 1699 cm^{-1}, which may be ascribed to a 2,2-dialkylcyclohexanone system.[2] With one mole of bromine, a monobromojatamansone, $C_{15}H_{25}OBr$ is formed, with carbonyl absorption at 1729 cm^{-1}, indicating an equatorially-oriented α-bromine atom. With excess bromine, only a dibromojatamansone is formed. Since the presence of a —CO—CH_2— group has been established, these results indicate that the other carbon atom adjacent to the carbonyl group is fully substituted.

* The material presented in this paper has been published in the form of two brief communications in *Tetrahedron Letters* No. 15, 5 (1959); *Chem. & Ind.* 1059 (1960).

[1] T. R. Govindachari, S. Rajadurai and B. R. Pai, *Chem. Ber.* **91**, 908 (1958).
[2] E. J. Corey, T. H. Topie and W. A. Wozniak, *J. Amer. Chem. Soc.* 77, 5415 (1955).

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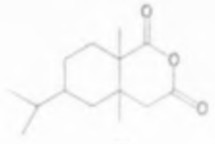
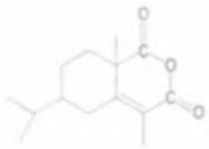
Pyrolysis of jatamansic acid yields norjatamansone, $C_{14}H_{24}O$ (III), showing carbonyl absorption at 1735 cm^{-1} (cyclopentanone). With excess benzaldehyde, norjatamansone gives a monobenzylidene derivative, yielding on ozonolysis, a

III

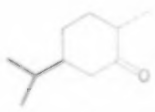


IV

diketone norjatamansadione, $C_{14}H_{22}O_2$ oxidized by sodium meta periodate to norjatamansic acid, $C_{14}H_{24}O_4$. The latter compound on heating with acetic anhydride yields norjatamansic anhydride (IV), having carbonyl bands at 1757 and 1805 cm^{-1} (glutaric anhydride). The anhydride on treatment with excess bromine yields only a monobromo derivative, $C_{14}H_{21}O_3Br$, which is converted by treatment with dimethylaniline to dehydronorjatamansic anhydride, $C_{14}H_{20}O_3$(λ_{max} 225 mμ, log ε, 3·67; infra-red bands at 1786, 1672 and 1595 cm^{-1}) which may be formulated as V. Dehydronorjatamansic anhydride dissolves in alkali, but acidification of the alkaline solution yields the anhydride directly, the isolation of the intermediate acid not being possible. The anhydride is recovered unchanged after prolonged treatment



V



VI

with ozone, from which it may be concluded that there is no terminal methylene group in the compound. This behaviour is consistent with the presence of a highly-hindered double bond as depicted in V.

Oxidation of jatamansic acid (or jatamansone) with manganese dioxide–sulphuric acid (60 per cent) yields trimellitic acid, whose formation should not involve any rearrangement prior to dehydrogenation, since jatamansic acid is recovered unchanged, together with some norjatamansone, under the same conditions in the absence of manganese dioxide.

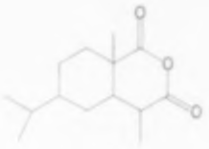
The results so far outlined offer clear proof that jatamansone contains two six-membered rings which are 1:2-fused. The two rings cannot be 1:3-fused, since in that case any structure formulated for dehydronorjatamansic anhydride would violate Bredt's rule, in the absence of an exocyclic double bond.

Oxidation of dehydronorjatamansic anhydride with $KMnO_4$–$NaIO_4$ proceeds quantitatively with formation of 1-*trans*-carvomenthone, (VI), isolated as the semicarbazone. This experiment offers conclusive proof for structure V advanced for dehydronorjatamansic anhydride. From this it would appear that norjatamansic anhydride should itself be formulated as VII. However the formation of dehydronorjatamansic anhydride from norjatamansic anhydride by bromination and dehydrobromination must involve migration of a methyl group from an angular to a ring

[a] R. V. Lemieux, E. Rudolf, *Canad. J. Chem.* **33**, 1701, 1710 (1955).

position and norjatamansic anhydride should itself be represented correctly by IV and not VII for the following reasons:

(a) Dehydrogenation of norjatamansic acid with Pd/c at 300° yields pure 1,2-dimethyl-4-isopropylbenzene[4] and not 2-ethyl-1-methyl-4-isopropylbenzene which could be expected if norjatamansic anhydride has structure VII. Comparison of the dehydrogenation product is most conveniently effected through the crystalline sulphonamide derivatives.



VII

(b) Norjatamansone yields a liquid benzylidene derivative converted by ozonolysis to norjatamansadione, which exhibits a positive Zimmermann reaction, comparable in intensity to that given by jatamansone and norjatamansone. The dione shows a peak at 1418 cm^{-1} characteristic of a —CO—CH_2— group, which disappears in the product (norjatamansatrione) obtained from it by oxidation with selenium dioxide.

(c) The NMR spectrum of norjatamansic anhydride (in chloroform solution at 40 Mc) definitely favours structure IV and not VII. The key feature is the quartet of lines with τ values of 6·4, 6·8, 7·3 and 7·8. The four lines should correspond to the CH_2 group of IV adjacent to the carbonyl function, with a chemical shift between them caused by a rigid six-membered ring, i.e. there are really two hydrogens with τ values of 6·6 and 7·55 with a spin-spin splitting of 16 c/s. The intensity of the lines is also in better accord with this interpretation rather than when this quartet is ascribed to the feature —CH(—CH_3)—CO— present in VII.

The sequence of these degradation results leads unequivocally to structure I for jatamansone, which is the first and only example of a sesquiterpenoid compound with two angular methyl groups in a hydronaphthalene tenplate. Biogenetically it could arise from a normal eudalenoid precursor by migration of the ring methyl group to the adjacent angular position.

The absolute configuration at C(6) follows from that of l-*trans*-carvomenthone[5] to which it has been degraded. The rotatory dispersion curve[6] of jatamansone exhibits a strong negative Cotton effect and the angular methyl group at C(9) should be therefore β-oriented. Evidence for the nature of the ring fusion is being sought, after which a definite assignment of configuration at C(10) can be made.

We reported earlier[1] that dehydrogenation of jatamansol yielded a bluish violet azulene. This has now been purified by chromatography on paraffin-impregnated paper[7] and freed from blue, reddish violet and violet azulenes present in trace amounts. The purified azulene jatazulene, yields a T.N.B. adduct, m.p. 158°, different from the

[4] A. Klages, *Ber. Dtsch. Chem. Ges.* **39**, 2311 (1906).
[5] A. J. Birch, *Ann. Rep. Chem. Soc.* **47**, 192 (1950).
[6] C. Djerassi, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **78**, 6362 (1956).
[7] O. Knessl and A. Vlastiborova, *Coll. Czech. Chem. Comm.* **19**, 782 (1954).

T.N.B. adducts of any of the known azulenes obtained from sesquiterpenoid compounds.

The formation of an azulene from a naphthalenic precursor is unusual and should be due to the location of the hydroxyl group in jatamansol adjacent to a fully saturated carbon atom. An analogous case is the formation of chamazulene from dihydrocyclopyrethrosin acetate.[8] The absorption spectrum of jatazulene strongly indicates that it is a trisubstituted azulene, similar to Se-guiazulene. However, there is a depression of 30° in the mixed m.ps. of the respective T.N.B. adducts.

Although no direct comparison has been made, it is likely from the data presented by Křepinský *et al.*[9] that jatamansone and valeranone[10] are identical. Křepinský *et al.* on the basis of further independent and different experimental evidence[11] have also advanced two alternative structures, one of these being I which has been shown by our work to be uniquely assignable to jatamansone.

EXPERIMENTAL

Jatamansene. Jatamansol (15 g) in carbon tetrachloride (60 ml) was treated with phosphorus tribromide (6 g) for 20 min with stirring and the temp maintained between 0° and 10°. Next day the mixture was heated on a water-bath for 15 min then decomposed with ice and the carbon tetrachloride layer thoroughly washed with dil NaOH solution. The residue after removal of solvent was treated with aniline (30 g) and after leaving overnight was heated at 160–180° for 2 hr. Acetic acid (30 ml) was added and the mixture steam distilled. The steam distillate was repeatedly extracted with ether and the ether extract washed with dil HCl, water and finally with saturated $NaHCO_3$ solution. After the removal of solvent the residue was distilled *in vacuo* to give *jatamansene* (7 g), b.p. 106–108°/4 mm n_{20}^{D}: 1·487. $[\alpha]_{20}^{D}$: 81·83° (*c*: 2·20, $CHCl_3$) (Found: C, 87·3; H, 12·6 $C_{15}H_{28}$ requires: C, 87·4; H, 12·7%).

Ozonolysis of jatamansene

(a) Jatamansene (5 g) in ethyl acetate (20 ml) was ozonized to completion (3 hr). The solvent was removed *in vacuo* and the residue was heated with water (50 ml) and pure zinc dust (0·5 g) on a water-bath for 3 hr, extracted with ether and the ether extract washed with $NaHCO_3$ solution to remove acidic materials. The bicarbonate solution on acidification with conc HCl gave jatamansic acid (about 0·2 g), m.p. 233–235°. The ether solution was evaporated and the residue distilled *in vacuo* to give the *dialdehyde* (2·5 g), b.p. 138°/1 mm (Found: C, 76·0; H, 10·5 $C_{15}H_{26}O_2$ requires: C, 75·7; H, 10·9%).

The *dialdehyde* when heated under reflux (3 hr) with water containing a little conc HCl readily lost a molecule of water and gave an *α,β-unsaturated aldehyde*, b.p. 144°/1·2 mm (Found: C, 81·4; H, 10·7 $C_{15}H_{24}O$ requires: C, 81·8; H, 10·9%). It gave a red *2,4-dinitrophenyl hydrazone* (from methanol), m.p. 168° (Found: C, 63·3; H, 7·2 $C_{21}H_{28}N_4O_4$ requires: C, 63·0; H, 7·0%).

The above dialdehyde (0·2 g) was gently heated on a water bath with hydrogen peroxide (15%; 15 ml) for 6 hr, excess hydrogen peroxide decomposed by adding a pinch of platinum oxide and then diluted with water and extracted with ether. After the removal of solvent the acid was crystallized from absolute ether, m.p. 233–235° and found to be identical with jatamansic acid, (m.p. and mixed m.p.).

(b) Jatamansene (2 g) in ethyl acetate (15 ml) was oxidized to completion with ozone (2 hr). The ethy acetate solution was then concentrated *in vacuo* and the residue treated with hydrogen peroxide solution (15%; 30 ml) and heated on a water-bath for 6 hr and a pinch of platinum oxide added to decompose the excess hydrogen peroxide. It was then extracted with ether and the ether solution washed with saturated $NaHCO_3$ solution which on acidification gave jatamansic acid (1·2 g), m.p. 233–235°. $[\alpha]_{20}^{D}$: −40·0° (*c*: 2·43 $CHCl_3$).

[8] D. H. R. Barton and P. de Mayo, *J. Chem. Soc.* 150 (1957).

[9] J. Křepinský, V. Herout and F. Šorm, *Tetrahedron Letters* No. 3, 9 (1960).

[10] A. Stoll, E. Seebeck and D. Stauffacher, *Helv. Chim. Acta* **40**, 135 (1957); J. Křepinský, V. Herout and F. Šorm, *Chem. Listy* **52**, 1784 (1958).

[11] J. Křepinský, M. Romanuk, V. Herout and F. Šorm, *Tetrahedron Letters* No. 7, 9 (1960).

Dimethyljatamansate. To a solution of jatamansic acid (2 g) in methanol (20 ml) an ether solution of diazomethane (prepared from 15 g of nitrosomethyl urea) was added. After leaving overnight and working up as usual the *dimethyl ester* (1·5 g), b.p. 140°/1 mm, n_D^{20}: 1·470 was obtained (Found: C, 68·3; H, 9·8 $C_{17}H_{30}O_4$ requires: C, 68·5; H, 10·1%).

Benzylidene derivative of jatamansone

(a) A solution of jatamansone (5 g) and benzaldehyde (15 g) in absolute ether (50 ml) was saturated with dry HCl gas and left overnight. After removal of ether, the residue was refluxed with fused sodium acetate (20 g) and acetic acid (30 ml) for 4 hr and after excess benzaldehyde was removed by steam distillation was extracted with ether. After the removal of solvent, the *benzylidene derivative* (1·2 g) obtained was crystallized from methanol, m.p. 115°, $[\alpha]_{20}^{D}$: −172·2° (*c*: 2·032 $CHCl_3$) (Found: C, 85·3; H, 9·4 $C_{22}H_{30}O$ requires: C, 85·2; H, 9·7%).

(b) Jatamansone (2 g) in KOH solution (50%; 10 ml) was treated with benzaldehyde (3 g) in absolute alcohol (10 ml) and the mixture heated on a water-bath for 3 hr then diluted with water and the precipitated benzylidene compound (2 g) crystallized from methanol, m.p. 115°.

Ozonolysis of the benzylidene derivative. The above benzylidene derivative (5 g) in chloroform (15 ml) was ozonized to completion (5 hr). The solvent was removed *in vacuo* and the residue treated with hydrogen peroxide solution (30%; 20 ml) heated on a water bath for 12 hr and then filtered hot so as to remove benzoic acid. The acidic product was repeatedly washed with hot water and then crystallized from absolute ether, m.p. 233–235° (3 g) and found to be identical with jatamansic acid, (m.p. and mixed m.p.).

Attempted isomerization of jatamansone

(a) Dry HCl gas was passed through a solution of jatamansone (5 g) in absolute ether (50 ml) to saturation. The mixture was left for 48 hr, the ether removed *in vacuo* and the residue after washing with $NaHCO_3$ solution distilled *in vacuo* to give an oil (4·5 g), b.p. 108°/1 mm which was found to be identical with jatamansone.

(b) A solution of jatamansone (2 g) in H_2O_4 (57%; 30 ml) was heated under reflux for 12 hr and the product, worked up as usual, was identical with the starting material.

Bromination of jatamansone

(a) To jatamansone (2·2 g) in glacial acetic acid (25 ml) a solution of bromine (1·8 g) in acetic acid (10 ml) was added. After ½ hr the mixture was diluted with water and extracted with ether and the ether extract washed with dil $NaHCO_3$ solution. After the removal of solvent the residue was distilled *in vacuo* to give the *monobromo compound* (2 g), b.p. 148°/0·3 mm. It was crystallized from pet ether (b.p. 40–60°), m.p. 105° (Found: C, 59·8; H, 8·6 $C_{15}H_{25}OBr$ requires: C, 59·8; H, 8·3%).

(b) To jatamansone (2 g) in acetic acid (20 ml) a large excess of bromine (10 g) in acetic acid (20 ml) was added. After 5 days, the product was worked up as above and the *dibromo compound* (2 g) obtained distilled *in vacuo*, b.p. 145°/0·6 mm. (Found: C, 47·7; H, 6·4 $C_{15}H_{24}OBr_2$ requires: C, 47·3; H, 6·3%).

Attempted dehydrohalogenation of the above bromo compound

(a) Monobromojatamansone (2 g) in dimethylaniline (20 ml) was heated under reflux for 6 hr, the reaction mixture diluted with water and acidified with conc HCl (30 ml) and extracted with ether. After the removal of ether, the residue was distilled *in vacuo* to give jatamansone and not the unsaturated compound.

(b) The bromo compound after refluxing with 50% NaOH for 3 hr gave only jatamansone.

Jatamansane. To a mixture of jatamansone (5 g) in diethyleneglycol (80 ml) sodium metal (2·5 g) in small bits followed by hydrazine hydrate (85%; 5 ml) was added. After heating under reflux for 1 hr the condenser was removed and the mixture kept at 190–200° (internal temp) for 5 hr and then diluted with water and extracted with ether. After the removal of ether the residue was subjected to the above procedure once again and the product obtained distilled *in vacuo* to give *jatamansane* (3 g), b.p. 90°/0·5 mm n_D^{20}: 1·482 $[\alpha]_{20}^{D}$: +63·02° (*c*: 1·936 $CHCl_3$). (Found: C, 86·3; H, 13·52 $C_{15}H_{28}$ requires: C, 86·5; H, 13·5%).

Norjatamansone. Jatamansic acid (5 g) in acetic anhydride (30 ml) containing barium hydroxide (0·2 g) was taken up in a distillation flask and heated gently first to remove acetic anhydride (i.e. up to

150°), then the temp of the bath was raised to 400° when an oil (3·5 g) distilled over. This oil (3·5 g) in pyridine (25 ml) was treated with semicarbazide hydrochloride (3·5 g) and heated at 70° for 2 hr. After dilution with water, the precipitated *semicarbazone* (3·5 g) was crystallized from alcohol, m.p. 238–240°. (Found: C, 68·0; H, 10·5 $C_{15}H_{27}N_3O$ requires: C, 67·9; H, 10·2%). The semicarbazone (3·5 g) was decomposed by heating under reflux with 4 N H_2SO_4 (150 ml) for 24 hr. The mixture was extracted with ether and after removal of solvent the residue was distilled *in vacuo* to give *norjatamansone* (2 g), b.p. 110°/4 mm n_D^{20}: 1·4815, $[\alpha]_{20}^D$: +16·77°, *d*: 0·9729. (Found: C, 80·6; H, 11·3 $C_{14}H_{24}O$ requires: C, 80·7; H, 11·5%).

Bromonorjatamansone. Norjatamansone (2 g) in glacial acetic acid (25 ml) containing hydrobromic acid (2 ml) was added to a solution of bromine (1·8 g) in acetic acid (10 ml). After 3 hr the mixture was worked up as in the case of monobromojatamansone, to give the *bromonorjatamansone* (1·5 g), b.p. 138–140°/3 mm, n_D^{20}: 1·5150. (Found: C, 58·2; H, 8·2 $C_{14}H_{23}OBr$ requires: C, 58·5; H, 8·0%).

When the bromo compound was heated with dimethylaniline under reflux the expected α,β-unsaturated ketone was not formed, but only norjatamansone. The bromo compound was recovered unchanged after heating with 2,4-dinitrophenylhydrazine in acetic acid solution.[12]

Norjatamansol. To a suspension of lithium aluminium hydride (1 g) in absolute ether (50 ml) the above ketone (2 g) in absolute ether (20 ml) was added with stirring and left overnight. The reaction mixture was worked up as usual and the *alcohol* (1·8 g) obtained was crystallized from absolute ether, m.p. 115°. (Found: C, 80·2; H, 12·5 $C_{14}H_{26}O$ requires: C, 80·0; H, 12·4%).

Attempted dehydration of norjatamansol

(a) The method adopted for the preparation of jatamansene from jatamansol was applied but the starting material was recovered unchanged.

(b) A mixture of the above alcohol (1 g) and potassium hydrogen sulphate (5 g) was distilled *in vacuo* but the distillate was found to be starting material.

(c) A mixture of the alcohol (1 g) in 50% H_2SO_4 (20 ml) was heated under reflux for 1 hr. It was extracted with ether, and after the removal of solvent the residue was found to be starting material.

Benzylidene derivative of norjatamansone. A mixture of norjatamansone (2 g), 40% alcoholic KOH solution (10 ml), benzaldehyde (3 g) and water (5 ml) was heated on a water-bath for 3 hr and the mixture diluted with water and extracted with ether. After the removal of solvent the residue was distilled *in vacuo*. The initial fraction was benzaldehyde and the *benzylidene derivative* (1·2 g) distilled at 160°/0·2 mm $[\alpha]_{20}^D$: +184·9° (*c*: 2·866 $CHCl_3$). (Found: C, 85·4; H, 9·4 $C_{21}H_{28}O$ requires: C, 85·1; H, 9·4%).

Ozonolysis of the above benzylidene derivative

(a) The benzylidene derivative (2 g) in chloroform (15 ml) was ozonized to completion (2 hr). The chloroform was removed *in vacuo* and the residue was treated with water (20 ml) and zinc dust (0·2 g). The mixture was heated on a water-bath for 6 hr, extracted with ether and washed with $NaHCO_3$ solution to remove acidic materials. After the removal of solvent, the residue was distilled *in vacuo* to give the *norjatamansadione* (0·8 g), b.p. 140°/0·3 mm. (Found: C, 75·3; H, 9·9 $C_{14}H_{22}O_2$ requires: C, 75·7; H, 9·9%).

To the above diketone (0·5 g) in alcohol (100 ml) potassium periodate (0·75 g) in water (250 ml) and 2 N H_2SO_4 (25 ml) was added. After keeping at room temp for 72 hr the mixture was extracted with ether and the ether solution then extracted with saturated $NaHCO_3$ solution (20 ml), which on acidification gave *norjatamansic acid* (0·2 g), m.p. 143°, $[\alpha]_{20}^D$: +49·9° (*c*: 1·98 $CHCl_3$). (Found: C, 65·2; H, 9·1 $C_{14}H_{24}O_4$ requires: 65·6, H, 9·4%).

(b) The benzylidene derivative (1 g) in chloroform (10 ml) was ozonized to completion (1 hr). After the removal of solvent, the residue was treated with hydrogen peroxide solution, (30%; 30 ml) heated on a water bath for 12 hr and the hot solution decanted from the viscous oil. The viscous mass was repeatedly washed with hot water to remove benzoic acid and then crystallized from dil methanol to give norjatamansic acid (0·4 g), m.p. 143°.

Selenium dioxide oxidation of norjatamansadione. The dione (1 g) in glacial acetic acid (30 ml) was refluxed with freshly sublimed selenium dioxide (0·6 g) for 4 hr and the mixture left overnight. The

[12] C. Djerassi and D. Marshall, *J. Amer. Chem. Soc.* **80**, 3986 (1958).

precipitated selenium was filtered off, the solvent removed *in vacuo* and the residue taken up in ether and the neutral fraction separated by the usual procedure. After removal of the solvent the residue was passed through a column of silver oxide and alumina using pet ether as eluent. After removal of the solvent the residue was distilled *in vacuo* to give *norjatamansatrione* (0·3 g), b.p. 155–160°/0·3 mm. (Found: C, 70·8; H, 8·6 $C_{14}H_{20}O_3$ requires: C, 71·2; H, 8·5%).

Norjatamansic anhydride. Norjatamansic acid (3 g) was refluxed with acetic anhydride (20 ml) for ½ hr, the acetic anhydride removed by distillation and the residue distilled *in vacuo* to give *norjatamansic anhydride* (2·5 g), b.p. 150°/0·1 mm. The distillate solidified and was crystallized from pet ether, (b.p. 40–60°), m.p. 85–86° $[\alpha]_{30}^{D}$: +38·95° (*c*: 2·22 $CHCl_3$). (Found: C, 70·9; H, 9·0 $C_{14}H_{22}O_3$ requires: C, 70·6, H, 9·3%).

Bromonorjatamansic anhydride. A mixture of the above anhydride (1·2 g) and bromine (0·3 ml) was heated in a sealed tube at 130° for 2 hr, extracted with benzene and the solvent removed *in vacuo*, The residue was crystallized from benzene–pet ether (b.p. 40–60°) to give the *bromo anhydride* (1·3 g). m.p. 143°, $[\alpha]_{30}^{D}$: +38·33° (*c*: 2·09 $CHCl_3$). (Found: C, 52·8; H, 6·8 $C_{14}H_{21}O_3Br$ requires: C, 53·0; H, 6·6%).

Dehydronorjatamansic anhydride. A mixture of the bromo anhydride (0·5 g) and dimethylaniline (5 ml) was heated at 150–160° for 3 hr and then poured on to crushed ice containing HCl and extracted with ether. The ether extract was repeatedly washed with dil HCl, water and dried (Na_2SO_4). After the removal of solvent the product was crystallized from benzene–pet ether to give the *dehydronorjatamansic anhydride* (0·35 g), m.p. 153°, $[\alpha]_{30}^{D}$: +186·7° (*c*: 2·09 $CHCl_3$). (Found: C, 71·6; H, 8·5 $C_{14}H_{20}O_3$ requires: C, 71·2; H, 8·5%).

Oxidation of jatamansone with manganese dioxide and sulphuric acid. To a mixture of jatamansone (5 g) and H_2SO_4 (57%; 20 ml) heated under reflux manganese dioxide (80 g) was added during the course of 5 hr and the heating continued for 18 hr. The mixture was then filtered and the manganese dioxide residue washed with hot water and the filtrate repeatedly extracted with ether. After the removal of ether the acid (0·3 g) was crystallized from acetone–benzene mixture, m.p. 216–218°. The acid was found to be identical with trimellitic acid (m.p. and mixed m.p.). (Found: C, 51·5; H, 3·2 $C_9H_6O_6$ requires: C, 51·4; H, 2·9%).

The imide prepared in the usual way was crystallized from alcohol, m.p. 255–257°. (Found: C, 56·5; H, 2·4 Calc. for $C_9H_5NO_4$: C, 56·5; H, 2·6%).

The anhydride of the acid was obtained by heating the acid above the m.p. and keeping it at that temperature for 5 min, m.p. 172°.

Both jatamansic acid and jatamansene on oxidation with manganese dioxide as in the above procedure gave trimellitic acid.

Dehydrogenation of norjatamansic acid. Norjatamansic acid (1 g) was intimately mixed with 30% palladized charcoal (0·6 g) and heated in a sealed tube at 310–320° for 30 hr. It was then extracted with ether and after the removal of solvent, the residual oil passed through a column of alumina using pet ether (40–60°) as eluent. After the removal of solvent the residue (0·5 g) was distilled, b.p. 190°. The distillate (0·2 g) dissolved in chloroform (3 ml) was treated with chlorosulphonic acid (1 g) with ice cooling. After about 20 min the mixture was poured into ice and extracted with chloroform and dried (Na_2SO_4). After the removal of solvent, the residue was mixed with ammonium carbonate (4 g), heated on a water-bath for ½ hr, water added and the product extracted with ether. The residue, after removal of solvent, was chromatographed (in chloroform) and crystallized from dil methanol, m.p. 158–160° and found to be identical with the *sulphonamide derivative* of 1,2-dimethyl-4-isopropylbenzene (m.p. and mixed m.p. and I.R.). (Found: C, 58·4; H, 7·5 $C_{11}H_{17}O_2NS$ requires: C, 58·2; H, 7·5%).

Oxidation of the dehydrogenation product with manganese dioxide and sulphuric acid. The above oil (1 g) dissolved in 57% sulphuric acid (45 ml) was heated under reflux and manganese dioxide (25 g) was added in small amounts during the course of 4 hr and heating continued for another 6 hr. It was then filtered, the residue washed with hot water, and the filtrate extracted repeatedly with ether. The ether solution was extracted with saturated $NaHCO_3$ solution and the alkaline solution on acidification gave an acid which was extracted with ether. After removal of ether, the acid (0·2 g) was crystallized from acetone–benzene mixture, m.p. 216° and found to be identical with trimellitic acid (m.p. and mixed m.p.).

Synthesis of 1-*methyl*-2-*ethyl*-4-*isopropylbenzene*. 2-Methyl-5-isopropylacetophenone[13] (10 g) in

[13] Ad. Claus, *Ber. Dtsch. Chem. Ges.* **19**, 230 (1886).

conc HCl (200 ml) was refluxed with zinc amalgam (45 g), with the addition of HCl (5 ml) every ½ hr for 48 hr. It was then worked up as usual and the hydrocarbon distilled at 210–212°, which gave a crystalline *sulphonamide derivative*, m.p. 136–137°. (Found: C, 59·8; H, 8·0 $C_{12}H_{19}SO_2N$ requires: C, 59·8; H, 7·9%).

1,2-*Dimethyl*-4-*isopropylbenzene*. 1-Methyl-2-chloromethyl-4-isopropylbenzene (10 g) was added slowly to a suspension of magnesium (1·2 g) in ether (30 ml). The mixture was refluxed for 3 hr and the resulting complex decomposed with water. The product was worked up as usual and the hydrocarbon (7 g) distilled at 190–192°. It gave a crystalline *sulphonamide derivative* (from methanol), m.p. 158°. (Found: C, 58·0; H, 7·3 $C_{11}H_{17}O_2NS$ requires: C, 58·2; H, 7·5%).

Sodium periodate oxidation of dehydronorjatamansic anhydride. A solution of dehydronorjatamansic anhydride (0·48 g) in aqueous pyridine (33%; 150 ml) was treated with a solution of sodium metaperiodate (0·7 g), potassium permanganate (15 mg) in aqueous pyridine (33%; 30 ml) and a solution of potassium carbonate (0·25%; 20 ml). The mixture was shaken for 30 hr, acidified with sulphuric acid and extracted with ether. After the removal of solvent, the residue was characterized as the *semicarbazone*, m.p. 193° (from ethanol) $[\alpha]_{589}^{D}$: −16·04 (*c*: 2·0 $CHCl_3$). (Found: C, 62·4; H, 10·0 $C_{11}H_{21}ON_3$ requires: C, 62·6; H, 10·0%). It was found to be identical with 1-*trans*-carvomenthone semicarbazone (m.p. and mixed m.p. and I.R.).

Jatazulene[5]

Paper chromotagraphy of jatazulene. The jatazulene obtained by the dehydrogenation of jatamansol was found by paper chromotagraphy to be a mixture of azulenes which were separated as follows:

Whatman No. 1 paper was impregnated with liquid paraffin (1·08 mg/cm²) by soaking in 5% solution of paraffin in pet ether (b.p. 40–60°), pressing between the folds of the same type of paper and finally air drying. The mixture of azulenes (30 mg) were placed in a horizontal line about 6 cm from the bottom of the paper and then hung vertically in a glass jar. The chromotagraphy was carried out by the upward irrigation method using 55% phosphoric acid, in a narrow trough below the paper and the acid level adjusted to 3 to 4 cm below the line of azulene. After 48 hr four distinct bands were obtained having the following R_f values:

Blue	R_f: 0·02
Bluish violet	R_f: 0·108
Red	R_f: 0·22
Violet	R_f: 0·30

Each band was cut out and shaken with water and pet ether in a separating funnel till the paper was converted to a pulp. The pet ether extract from each band was extracted with 90% phosphoric acid and the phosphoric acid layer washed with pet ether to remove any non azulenic materials. The azulenes were regenerated from the acid extracts on dilution with water, and extracted with pet ether. After the removal of solvent, the azulenes were passed through a column of alumina using pet ether as eluent. The azulenes obtained from blue, red and violet bands were too small to be characterized. The bluish violet band gave a T.N.B. adduct from methanol (10 mg), m.p. 158°, visible spectrum max 562 and 582 m (cyclohexane). (Found: C, 61·7; H, 5·1. $C_{21}H_{23}N_3O_6$ requires: C, 61·3; H, 5·1%).

Acknowledgement—We are deeply grateful to Dr. N. Sheppard for measurement and interpretation of the N.M.R. spectrum of norjatamansic anhydride and to Prof. Carl Djerassi for measurement and interpretation of the rotatory dispersion curve of jatamansone. We thank the Government of India for a National Research Fellowship (to S. R.) and the Government of Madras for a Research Assistantship (to K. K. P.).

Tetrahedron, 1961, Vol. 12, p. 113. Pergamon Press Ltd. Printed in Northern Ireland

VOL. 12 1961

ERRATA

1. B. A. PORAI-KOSHITS: The structure of aromatic diazo-compounds, *Tetrahedron* **11**, 30–38 (1960).

p. 31, line 13: for "$K_a'K_5 \gg K_w$" read "$K_aK_5K_w$"

p. 31, line 15: for "$\frac{K_w^{2'}}{K_w} \gg \frac{K_a''}{K_b}$" read "$\frac{K_a'}{K_w} \gg \frac{K_a}{K_b}$"

p. 31, line 21: for "$K_a = \frac{C \cdot K[H^+]I}{[H^+]_1^3 - 2C \cdot K}$ and $K_b = \frac{C \cdot K_w[H^+]I}{[H^+]_1^3 - 2C \cdot K}$"

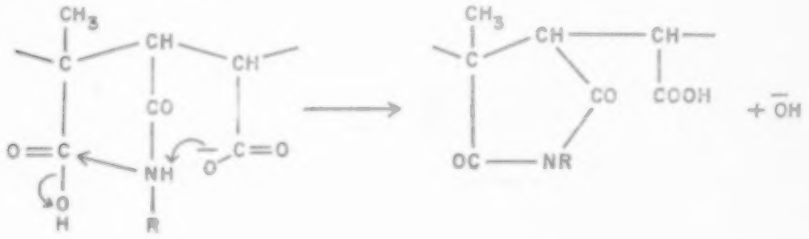
read "$K_a = \frac{C \cdot K[H^+]_1}{[H^+]_1^3 - 2CK}$ and $K_b = \frac{C \cdot K_w[H^+]_1}{[H^+]_1^3 - 2CK}$"

p. 31, line 23: delete the wording "for water".

p. 36, 1st equation; p. 37, 1st equation: for "$R - N_2O$" read "$R - N_2O^-$"

2. P. MADHAVAN NAIR, R. SRINIVASAN and K. VENKATARAMAN: Condensation of 2,4-dinitrochlorobenzene with *o*-hydroxyarylamides, *Tetrahedron* **11**, 140–147 (1960).

The authors have requested that the following formula be substituted for that published at the top of p. 142.



Tetrahedron, 1961, Vol. 12, pp. 114 to 115. Pergamon Press Ltd. Printed in Northern Ireland

A list of some of the papers to be published in future issues

N. PETRAGNANI: Aryl tellurium trihalides—II. Condensation reaction with methylketones and aromatic compounds containing electron-repelling groups.

KATSUMI KOTERA: The stereochemistry of lycorane-III (−)β-lycorane.

KATSUMI KOTERA: The stereochemistry of lycorane-III γ- and β-lycorane.

J. W. POWELL and M. C. WHITING: The decomposition of sulphonhydrazone salts: mechanism and stereochemistry—II. The pyrolysis of the diazodecalins.

J. W. POWELL and M. C. WHITING: The analysis of mixtures of octalines.

H. C. BROWN: Hydroboration—a powerful synthetic tool.

K. AGHORAMURTHY, K. G. SARMA and T. R. SESHADRI: Chemical investigations of Indian lichens—XXIV. The chemical components of *Alectoria virens* Tayl. Constitution of a new depsidone, nirensic acid.

WATARU NAGATA: Totalsynthetische Untersuchungen an Steroiden—VII. Einführung der C-Substituenten in die angulare Stellung der kondensierten Ringsysteme (Teil 2). Degradative Darstellung der rac. D-Homo-18-norandrostan-3β-ol-17-on-13β- sowie 13α-Carbonsäure.

WATARU NAGATA: Totalsynthetische Untersuchungen an Steroiden—VIII. Einführung der C-Substituenten in die angulare Stellung der kondensierten Ringsysteme (Teil 3). Einwirkung von Kaliumcyanid unter Zusatz von Ammoniumchlorid auf rac. D-Homo-18-norandrostanderivative.

WATARU NAGATA: Totalsynthetische Untersuchungen an Steroiden—IX. Einführung der C-Substituenten in die angulare Stellung der kondensierten Ringsysteme (Teil 4). Darstellung von rac. D-Homo-18-oxoandrostan-3β-ol-17-on.

WATARU NAGATA, TADAO TERASAWA, SHOICHI HIRAI and KEN'ICHI TAKEDA: Totalsynthetische Untersuchungen an Steroiden—X. Totalsynthese von rac. 5α-Preg-16-en-20-on-3β-ol-3-acetat und rac. 16-Acetyl-androst-16-en-3β-ol-3-acetat.

G. H. KULKARNI, A. PAUL, A. SOMASEKAR RAO, G. R. KELKAR and S. C. BHATTACHARYYA: Terpenoids—XXIV. Isolation of 12-methoxy dihydrocostunolide from costus root oil.

T. MATSUURA, T. KAMIKAWA and T. KUBOTA: Natural furan derivatives—VIII. Relationship between the furan ring and six- and seven-membered lactone rings in obacunone.

T. KAMIKAWA and T. KUBOTA: Natural furan derivatives—VII. The presence of a seven-membered α,β-unsaturated lactone in obacunone.

PING-YUAN YEH and PIH-KUEI HUANG: Malvidin 3-galactoside and delphinidin 7-galactoside *Bladhia sieboldii*.

S. K. BALASUBRAMANIAN: Studies in stereochemistry—I. Stereospecific routes to *trans*-anti- and *cis*-syn-Δ^5-dodecahydrophenanthrenes.

A. JULG: Théorie du pouvoir rotatoire naturel dans la méthodes des orbitales moleculaires.

G. W. K. CAVILL, P. S. CLEZY and F. B. WHITFIELD: The chemistry of mould metabolites—IV. Reductive acetylation and reoxidation of some phenoxazin-3-ones.

C. A. COULSON: Bond lengths in the cyclo-octatetraene dianion C_8H_8.

W. G. DAUBEN and R. L. CARGILL: Photochemical transformations—VI. Isomerization of cycloheptadiene and cycloheptatriene.

VOL.
12
1961

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HYDROBORATION—A POWERFUL SYNTHETIC TOOL*

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(*Received* 7 *October* 1960)

EARLY observations on the reaction of diborane with unsaturated organic compounds indicated that the reaction required either elevated temperatures or long reaction times,[1–4] and did not provide a convenient synthetic route to the organoboranes. In the course of studying the reducing action of sodium borohydride–aluminum chloride solutions on representative organic molecules,[5] it was observed that unsaturated molecules such as ethyl oleate utilized more than the two "hydrides" required for reduction of the ester grouping. Investigation of the phenomenon revealed that the reagent readily reacts with olefins to convert them into the corresponding organoboranes (1).[6]

$$9RCH{=}CH_2 + 3NaBH_4 + AlCl_3 \xrightarrow{\text{Diglyme}^\dagger} 3(RCH_2CH_2)_3B + AlH_3 + 3NaCl \quad (1)$$

Investigation soon uncovered alternative convenient procedures for the conversion of olefins into organoboranes (2,3).[7]

$$12RCH{=}CH_2 + 3NaBH_4 + 4BF_3 \xrightarrow{\text{Diglyme}} 4(RCH_2CH_2)_3B + 3NaBF_4 \quad (2)$$

$$6RCH{=}CH_2 + B_2H_6 \xrightarrow[\text{or EE}]{\text{THF}^\ddagger} 2(RCH_2CH_2)_3B \quad (3)$$

These reactions are rapid and quantitative at room temperature. They make the organoboranes readily available as intermediates for the synthetic chemist and stimulate a new interest in the chemistry of these reactive compounds.

Although the reactions of organoboranes will be reviewed later in this discussion, it is necessary to call attention to the simple oxidation of organoboranes with alkaline hydrogen peroxide (4).[6–8]

$$R_3B + 3H_2O_2 + NaOH \rightarrow 3ROH + NaB(OH)_4 \quad (4)$$

The reaction is essentially quantitative, and appears to proceed without rearrangement, placing an hydroxyl group at the precise position previously occupied by the boron atom in the organoborane. Consequently, it has been of immense value in studying this conversion of olefins into organoboranes.

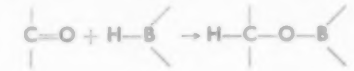
* Lecture to the Organic Division at the 137th Meeting of the American Chemical Society in Cleveland, Ohio, April 12, 1960, in connection with the 1960 A.C.S. Award for Creative Work in Synthetic Organic Chemistry.

† Diglyme: diethyleneglycol dimethyl ether; triglyme: triethyleneglycol dimethyl ether.

‡ THF : tetrahydrofuran. EE: ethyl ether.

[1] D. T. Hurd, *J. Amer. Chem. Soc.* **70**, 2053 (1948).
[2] F. G. A. Stone and H. J. Emeleus, *J. Chem. Soc.* 2755 (1950).
[3] A. T. Whatley and R. N. Pease, *J. Amer. Chem. Soc.* **76**, 835 (1954).
[4] F. G. A. Stone and W. A. G. Graham, *Chem. & Ind.* 1881 (1955).
[5] H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.* **78**, 2582 (1956).
[6] H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.* **78**, 5694 (1956); **81**, 6423 (1959).
[7] H. C. Brown and B. C. Subba Rao, *J. Org. Chem.* **22**, 1136 (1957); *J. Amer. Chem. Soc.* **81**, 6428 (1959).
[8] J. R. Johnson and M. G. Van Campen, Jr. *J. Amer. Chem. Soc.* **60**, 121 (1938).

The addition of the boron–hydrogen bond to multiple linkages of carbon to oxygen, to nitrogen and to carbon, appears to be a general reaction (5–7), as general as the related older reaction involving the addition of hydrogen to these systems.



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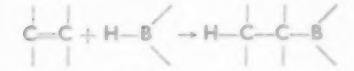


(7)

Whereas the addition of hydrogen generally requires elevated temperatures and catalysts, the addition of the boron–hydrogen bond generally proceeds quite rapidly at room temperature in ether solvents. The term hydroboration (HB) has been suggested as a general term to refer to the addition of the boron-hydrogen bond to multiple linkages. The present discussion will be restricted to the hydroboration of olefins and acetylenes.

Hydroboration procedures

Sodium borohydride is essentially insoluble in ethyl ether and tetrahydrofuran, but it is readily soluble in diglyme. Consequently this is the solvent of choice when sodium borohydride is the hydroborating agent. The most convenient procedure is to mix the sodium borohydride with the olefin in diglyme and to add boron trifluoride etherate slowly (exothermic reaction) from a dropping funnel, maintaining an inert atmosphere. The reaction is essentially complete immediately following completion of addition (8).

In many cases where the organoborane is desired simply as an intermediate for further reaction it need not be isolated. Thus it can be oxidized *in situ* with alkaline hydrogen peroxide to the alcohol, which is then readily recovered from the reaction mixture by distillation. In cases where the alcohol desired possesses a boiling point inconveniently near that of diglyme (b.p. 162°), the related solvent, triglyme (b.p. 216°), can be utilized.

Alternatively, diborane may be readily prepared by treating sodium borohydride with boron trifluoride etherate[9] and the gas passed into a solution of the olefin in tetrahydrofuran* (9). Or a solution of diborane in tetrahydrofuran may be prepared and the olefin added slowly (exothermic reaction) to the solution. These latter procedures yield the pure organoborane in the volatile solvent tetrahydrofuran, and a simple distillation suffices to isolate the organoborane in a state of high purity.

The unavailability of diglyme abroad has led to difficulties in applying these procedures.[10,11] Fortunately, over the years numerous procedures have been developed for the preparation of diborane and the information accumulated makes it possible to circumvent the requirement for any particular solvent or reagent.[12]

* Tetrahydrofuran is preferred because of the high solubility of diborane in the solvent.

[9] H. C. Brown and P. A. Tierney, *J. Amer. Chem. Soc.* **80**, 1552 (1958).
[10] R. Dulou and Y. Chrétien-Bessière, *Bull. Soc. Chim. Fr.* **9**, 1362 (1959).
[11] S. Wolfe, M. Nussim, Y. Mazur and F. Sondheimer, *J. Org. Chem.* **24**, 1034 (1959).
[12] H. C. Brown, K. J. Murray, L. J. Murray, J. A. Snover and G. Zweifel, *J. Amer. Chem. Soc.* **82**, 4233 (1960).

Thus the reaction of lithium aluminum hydride with boron trifluoride etherate can be used to accomplish hydroboration (10).[10,11] Similarly, lithium borohydride is soluble in both ethyl ether and tetrahydrofuran and can be utilized in these solvents (11).[12] Sodium borohydride, although essentially insoluble in tetrahydrofuran, reacts readily with boron trifluoride etherate and olefin in this medium to produce the organoborane (12).[12] Even ethyl ether can be utilized with sodium borohydride—a small quantity of anhydrous zinc chloride serves to catalyze the hydroboration of olefins by sodium borohydride in ethyl ether suspension (13).[12] Finally, in tetrahydrofuran suspension potassium borohydride reacts with lithium chloride to form lithium borohydride in solution[13] and the latter can be utilized readily for hydroboration (14).[12]

Boron trifluoride etherate is generally applicable as the acid component for these hydroborations. However, it can be replaced by boron trichloride (15),[12] or by a mixture of aluminum chloride and methyl borate (16).[12] Finally, a solution of sulfuric acid in the ether solvent likewise serves to accomplish the hydroboration reaction (17).[12]

The above procedures permit the hydroboration of olefins under mild conditions, 0 to 25°. In cases where elevated temperatures can be tolerated, hydroboration may be accomplished by heating the olefin with amine-boranes at temperatures of 100–200° (18)[14,15] or with triisobutylborane (19).[16]

$$12RCH{=}CH_2 + 3NaBH_4 + 4BF_3 \xrightarrow{\text{diglyme}} 4(RCH_2CH_2)_3B + 3NaBF_4 \quad (8)$$

$$3NaBH_4 + 4BF_3 \xrightarrow{\text{diglyme}} 2B_2H_6\uparrow + 3NaBF_4$$

$$6RCH{=}CH_2 + B_2H_6 \xrightarrow{\text{THF}} 2(RCH_2CH_2)_3B \quad (9)$$

$$12RCH{=}CH_2 + 3LiAlH_4 + 4BF_3 \xrightarrow{\text{EE}} 4(RCH_2CH_2)_3B + 3LiAlF_4 \quad (10)$$

$$12RCH{=}CH_2 + 3LiBH_4 + BF_3 \xrightarrow{\text{EE}} 4(RCH_2CH_2)_3B + 3LiF \quad (11)$$

$$12RCH{=}CH_2 + 3NaBH_4(\text{susp.}) + 4BF_3 \xrightarrow{\text{THF}} 4(RCH_2CH_2)_3B + 3NaBF_4 \quad (12)$$

$$12RCH{=}CH_2 + 3NaBH_4(\text{susp.}) + 4BF_3 \xrightarrow[10\%\ ZnCl_2]{\text{EE}} 4(RCH_2CH_2)_3B + 3NaBF_4 \quad (13)$$

$$KBH_4(\text{susp.}) + LiCl \xrightarrow{\text{THF}} LiBH_4 + KCl\downarrow$$

$$12RCH{=}CH_2 + 3LiBH_4 + BF_3 \xrightarrow{\text{THF}} 4(RCH_2CH_2)_3B + 3LiF \quad (14)$$

$$12RCH{=}CH_2 + 3NaBH_4 + BCl_3 \xrightarrow{\text{diglyme}} 4(RCH_2CH_2)_3B + 3NaCl \quad (15)$$

$$12RCH{=}CH_2 + 3NaBH_4 + AlCl_3 + B(OCH_3)_3 \xrightarrow{\text{diglyme}} 4(RCH_2CH_2)_3B + 3NaCl + Al(OCH_3)_3 \quad (16)$$

$$6RCH{=}CH_2 + 2NaBH_4 + H_2SO_4 \xrightarrow{\text{diglyme}} 2(RCH_2CH_2)_3B + Na_2SO_4 + H_2 \quad (17)$$

$$3RCH{=}CH_2 + (C_2H_5)_2N{:}BH_3 \rightarrow (RCH_2CH_2)_3B + (C_2H_5)_3N \quad (18)$$

$$3RCH{=}CH_2 + [(CH_3)_2CHCH_2]_3B \rightarrow (RCH_2CH_2)_3B + 3(CH_3)_2C{=}CH_2 \quad (19)$$

[13] R. Paul and N. Joseph, *Bull. Soc. Chim. Fr.* 550 (1952).
[14] M. F. Hawthorne, *J. Org. Chem.* **23**, 1788 (1958).
[15] E. C. Ashby, *J. Amer. Chem. Soc.* **81**, 4791 (1959).
[16] R. Köster, *Liebigs Ann.* **618**, 31 (1958).

Scope and stoichiometry[7]

The hydroboration reaction has now been applied to an enormous number of olefins of widely different structures. In practically all cases hydroboration proceeds simply and rapidly at room temperature. Representative olefins which have been utilized in this reaction include:

Terminal olefins: 1-hexene, 1-octene, 1-decene, 1-tetradecene, 3-methyl-1-butene, 3,3-dimethyl-1-butene, 4,4-dimethyl-1-pentene, 2-methyl-1-butene, 2-methyl-1-pentene and 2,4,4-trimethyl-1-pentene.

Dialkyl internal olefins: 2-hexene, 3-hexene, 2-octene, *cis*- and *trans*-4-methyl-2-pentene, *cis*- and *trans*-4,4-dimethyl-2-pentene, and *trans*-2,2,5,5-tetramethyl-3-hexene.

Cyclic olefins: cyclopentene, cyclohexene, and norbornene.

Trialkyl olefins: 2-methyl-2-butene, 2-methyl-2-pentene, 3-ethyl-2-pentene, 2,4,4-trimethyl-2-pentene, 1-methylcyclopentene, 1-methylcyclohexene and α-pinene.

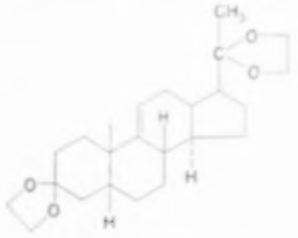
Tetraalkyl olefins: 2,3-dimethyl-2-butene, 1,2-dimethylcyclopentene and 1,2-dimethylcyclohexene.

Aryl olefins: styrene, α-methylstyrene, 1-phenylcyclohexene, 1,1-diphenylethylene, *trans*-stilbene and triphenylethylene.

Substituted olefins: vinyl chloride, allyl chloride, allyl ethyl ether, ethyl oleate and ethyl cinnamate.

The hydroboration reaction has also been applied to a wide variety of acetylenes and dienes. Since these offer a number of points of special interest, this topic will be considered later.

In only one case to date has it been noted that a double bond resists the hydroboration reaction. Wechter reported that 3,20-biscycloethylenedioxy-5β-pregn-9(11)-ene failed to undergo hydroboration under the usual hydroboration conditions (20).[17]



$$\xrightarrow{HB} \text{No reaction} \qquad (20)$$

On the other hand, the analogous compound with the A/B-*trans* junction does undergo hydroboration (21).[18]

(21)

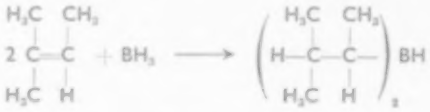
[17] W. J. Wechter, *Chem. & Ind.* 294 (1959).
[18] F. Sondheimer and M. Nussim, *Chem. & Ind.* 400 (1960).

The available data support the conclusion that hydroboration is a general reaction of the carbon–carbon double bond with only the most hindered olefins exhibiting any resistance to the addition.

In the case of simple olefins, the reaction commonly proceeds rapidly to the complete utilization of the active hydrogen of the diborane molecule, with the formation of the trialkylborane (22).

(22)

However, trisubstituted olefins, such as 2-methyl-2-butene and 1-methylcyclohexene, react rapidly at room temperature to utilize only two of the active hydrogens of the borane group, yielding a dialkylborane (or its dimer) as the reaction product (23).



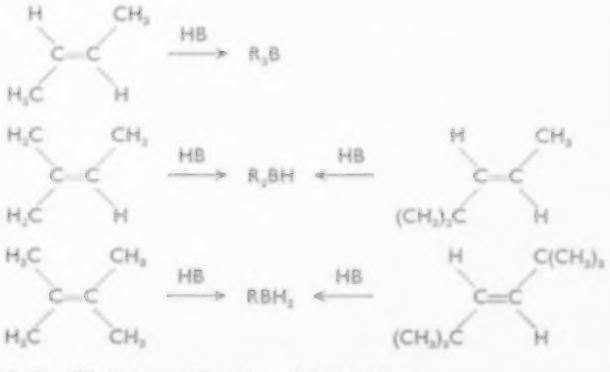
(23)

Although further reaction to the trialkylborane stage is possible, the reaction is very slow at room temperature, requiring extended periods of time for completion.

Finally, tetrasubstituted olefins, such as tetramethylethylene, react rapidly only to the first stage.

(24)

This phenomenon appears to be largely steric in origin. Thus if the double bond is loaded with groups of much larger steric requirements, such as t-butyl, the hydroboration tends to become quite slow at even earlier stages. For example, *trans*-t-butylmethylethylene undergoes hydroboration rapidly only to the dialkylborane stage,[19] while the corresponding reaction of *trans*-di-t-butylethylene appears to halt at the monoalkylborane stage (25).[20]



(25)

[19] H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.* **82**, 1504 (1960).
[20] T. J. Logan and T. J. Flautt, *Ibid.* **82**, 3446 (1960).

Directive effects[19]

The hydroboration of 1-hexene yields an organoborane which, upon oxidation with alkaline hydrogen peroxide, is converted quantitatively into a mixture of hexanols, 94 per cent 1- and 6 per cent 2-hexanol. It is concluded that the addition reaction has proceeded to place the boron atom predominantly at the terminal position, with only a minor amount of the reaction proceeding to place the boron in the 2- position. Similar results are observed with 1-butene, 1-pentene and 1-octene. Branching of the alkyl group, as in 3-methyl-1-butene and 3,3-dimethyl-1-butene, does not alter the distribution (Table 1).

TABLE 1. DIRECTIVE EFFECTS IN THE HYDROBORATION OF TERMINAL OLEFINS AT 20°

Olefin	Alcohol product, %	
	1-ol	2-ol
1-Butene	93	7
1-Pentene	94	6
1-Hexene	94	6
3-Methyl-1-butene	94	6
3,3-Dimethyl-1-butene	94	6
4,4-Dimethyl-1-pentene	93	7
p-Methoxystyrene	91	9
p-Methylstyrene	82	18
Styrene	80	20
p-Chlorostyrene	65	35
Allylbenzene	90	10
2-Methyl-1-butene	99	1
2,4,4-Trimethyl-1-pentene	99	1
α-Methylstyrene	100	trace

Essentially complete addition of the boron atom to the terminal position of disubstituted olefins, such as 2-methyl-1-butene and 2,4,4-trimethyl-1-pentene, is observed. Evidently the combined directive effect of the two alkyl substituents dominates the reaction.

The addition is less one-sided in the case of styrene, with 80 per cent of the boron in the terminal position and 20 per cent on the secondary carbon. Moreover, the direction of addition is strongly modified by substituents in the *para* position.

In the case of internal olefins containing two different alkyl groups there is little discrimination between the two carbon atoms of the double bond. This is true even in the case of molecules, such as *trans*-4-methyl-2-pentene and *trans*-4,4-dimethyl-2-pentene, where the two alkyl groups on the double bond differ markedly in their steric requirements. Only in the case of *trans*-1-phenylpropene, where the phenyl group is opposed to a methyl group, is a marked directive effect indicated, and here the boron atom actually prefers (85 per cent) the carbon atom holding the phenyl substituent.

Finally, in olefins containing three alkyl substituents on the double bond, such as 2-methyl-2-butene and 2,4,4-trimethyl-2-pentene, the addition proceeds to place the boron atom predominantly on the less substituted of the two carbon atoms of the double bond.

The data are summarized in Table 2.

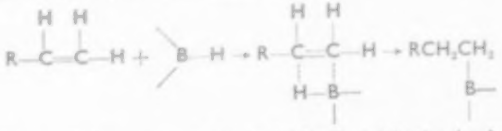
The results clearly show that a change in the bulk of the alkyl group attached to the double bond, as in "ethylethylene" (93 per cent 1-), "isopropylethylene" (94 per cent 1-) and t-butylethylene (94 per cent 1-), does not influence the direction of addition. Consequently, the results argue against steric control of the direction of addition. The marked influence of *para* substituents on the direction of addition likewise supports the conclusion that the direction of addition must be controlled primarily by electronic factors.

TABLE 2. DIRECTIVE EFFECTS IN THE HYDROBORATION OF INTERNAL OLEFINS AT 20°

Olefin	Alcohol product, % 2-ol	3-ol
cis-2-Pentene	55	45
trans-2-Pentene	51	49
cis-2-Hexene	50	50
trans-2-Hexene	46	54
cis-3-Hexene		100
trans-4-Methyl-2-pentene	57	43
trans-4,4-Dimethyl-2-pentene[a]	58	42
trans-1-Phenylpropene	85[b]	15[c]
2-Methyl-2-butene[a]	2	98[d]
2,4,4-Trimethyl-2-pentene[a]	2	98[e]

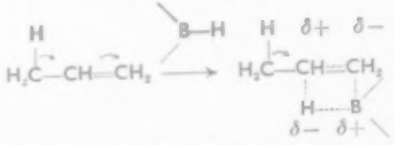
[a] Hydroboration to the dialkylborane stage.
[b] 1-Phenyl-1-propanol.
[c] 1-Phenyl-2-propanol.
[d] 3-Methyl-2-butanol.
[e] 2,4,4-Trimethyl-3-pentanol.

The available evidence supports the conclusion that the addition reaction must involve a simple four-center transition state (26).



(26)

The boron–hydrogen bond is presumably polarized, with the hydrogen having some hydridic character. In view of the electronic shifts generally utilized to account for the normal addition of hydrogen chloride to propylene, the preference of the boron atom for the terminal position is readily understood (27).

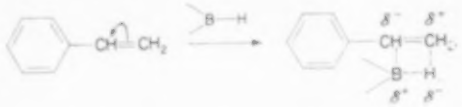


(27)

A similar discussion can be used to rationalize the observed preference of the boron atom for the terminal position of styrene (28).

(28)

It is generally recognized that a phenyl group cannot only serve to supply electrons to an electron deficient center, but it can also serve as an electron sink. This provides a simple explanation for the increased substitution in the *alpha* position observed in styrene (29).



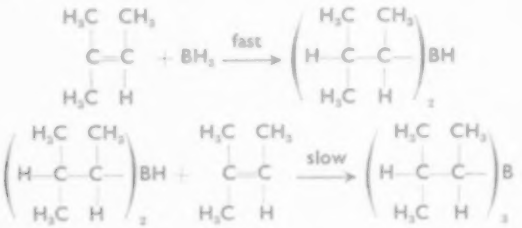
(29)

Electron withdrawing substituents, such as *p*-chloro, should stabilize, and electron supplying substituents, such as *p*-methoxy, should destabilize such a transition state. This is in accord with the influence of these substituents on the hydroboration of the substituted styrenes (Table 2).

At the present time there is little quantitative information on the influence of other substituents on the direction of the addition reaction. It is evident that major effects will be encountered. Thus trimethylvinylsilane undergoes hydroboration to place 37 per cent of the boron in the secondary position[21] as compared to 6 per cent for t-butylethylene.[19] This problem is currently under investigation in our laboratory.

Bis-3-methyl-2-butylborane as a selective hydroborating agent[22]

It was pointed out earlier that highly substituted olefins, such as 2-methyl-2-butene, undergo hydroboration rapidly to the dialkylborane stage, with further reaction to the trialkylborane stage being relatively slow (30).



(30)

The slowness of the last stage in this particular case, in contrast to the high speed with which other olefins undergo reaction to the trialkylborane stage, is presumably a result of the large steric requirements of the intermediate dialkylborane. It appeared that such a reagent might exhibit an enhanced sensitivity to the steric requirements of the substituents on double bonds and thereby exert a steric influence on the direction of hydroboration.

Bis-3-methyl-2-butylborane, conveniently synthesized by the hydroboration of 2-methyl-2-butene, was selected for study. 1-Hexene reacts rapidly with the reagent, and oxidation of the product yielded 1-hexanol in an isomeric purity of at least 99 per cent, in contrast with the 94 per cent isomeric purity realized with diborane itself. Similarly, styrene yielded less than 2 per cent of the secondary alcohol, whereas diborane results in the formation of 20 per cent. Finally, *cis*-isopropylmethylethylene yielded 97 per cent of the less hindered isomer, 4-methyl-2-pentanol.

The experimental data are summarized in Table 3.

[21] D. Seyferth, *J. Inorg. Nucl. Chem.* **7**, 152 (1958).
[22] H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.* **82**, 3222 (1960).

In the course of these studies it was noted that there was a vast difference in the ease with which different olefins reacted with the reagent. Thus, the reaction with 1-hexene was complete in a matter of minutes at 0°, whereas the reactions of internal olefins were much slower, with cyclopentene reacting faster than *cis*-2-hexene and the latter reacting considerably faster than cyclohexene. *Cis*-2-hexene reacted considerably faster than the *trans* isomer. Trisubstituted olefins, such as 2-methyl-2-butene and 1-methylcyclohexene, reacted very slowly.

TABLE 3. DIRECTIVE EFFECTS IN THE HYDROBORATION OF UNSYMMETRICAL OLEFINS WITH DIBORANE AND BIS-3-METHYL-2-BUTYLBORANE

Olefin	Hydroborating agent	Temp., °C	Time, hr	Alcohol distribution, % 1-ol	2-ol	3-ol
1-Hexene	Diborane	25	1	94	6	
	R_2BH	0	1	99	1	
Styrene	Diborane	25	1	80	20	
	R_2BH	25	2	98	2	
p-Methoxy-styrene	Diborane	25	1	91	9	
	R_2BH	25	2	98	2	
trans-4-Methyl-2-pentene	Diborane	25	1		57	43
	R_2BH	25	12		95	5
cis-4-Methyl-2-pentene	R_2BH	25	12		97	3

The results may be expressed in the following series: 1-hexene $\geq$ 3-methyl-1-butene $>$ 2-methyl-1-butene $>$ 3,3-dimethyl-1-butene $>$ *cis*-2-hexene $\geq$ cyclopentene $>$ *trans*-2-hexene $>$ *trans*-4-methyl-2-pentene $>$ cyclohexene $\geq$ 1-methylcyclopentene $>$ 2-methyl-2-butene $\geq$ 1-methylcyclohexene $\geq$ 2,3-dimethyl-2-butene.

The differences in reactivities are quite large and can be utilized for the selective hydroboration of a more reactive olefin in the presence of a less reactive structure. Thus, treatment of 1-pentene and 2-pentene with a controlled quantity of the reagent yielded the 2-pentene free of the 1-isomer. Similarly, a mixture of 1-hexene and cyclohexene yielded essentially pure cyclohexene. Treatment of an equimolar mixture of cyclopentene and cyclohexene yielded a product which was nearly pure cyclohexene, with only minor amounts of the more reactive cyclopentene remaining. Even more exciting, it proved possible to treat a commercial mixture of *cis*- and *trans*-2-pentene (18 per cent *cis*- and 82 per cent *trans*-) with the reagent, realizing a product which contained better than 97 per cent of the *trans* isomer.

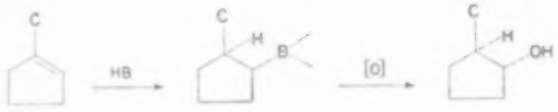
The reagent should be particularly useful to accomplish the selective hydroboration of complex molecules containing two or more reactive centers. Considerable success has been realized in this direction. It is evident that the reagent should be a very useful synthetic tool in the terpene and steroid fields.

Stereochemistry of hydroboration[23]

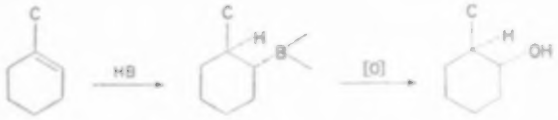
The hydroboration of cyclic olefins provides a means of observing the stereochemistry of the reaction. Thus, the hydroboration of 1-methylcyclopentene and

[23] H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.* **81**, 247 (1959).

1-methylcyclohexene, followed by oxidation with alkaline hydrogen peroxide, results in the formation of pure *trans*-2-methylcyclopentanol and *trans*-2-methylcyclohexanol. The available evidence indicates that the hydrogen peroxide oxidation proceeds with retention of configuration. Consequently, the hydroboration must involve a *cis*-addition of the hydrogen–boron bond to the double bond of the cyclic olefin (31).



(31)



The products in these hydrations are the thermodynamically stable isomers. However, this cannot be the controlling factor in the reaction since the hydroboration of 1,2-dimethylcyclopentene and 1,2-dimethylcyclohexene produces pure *cis*-1,2-dimethylcyclopentanol and *cis*-1,2-dimethylcyclopentanol, both of which are the thermodynamically less stable isomers (32).

(32)

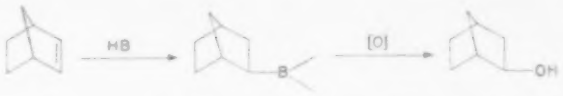
This *cis* hydration has been utilized to achieve a convenient synthesis of diastereomeric alcohols (33,34).[24]

(33)

(34)

[24] E. L. Allred, J. Sonnenberg and S. Winstein, *J. Org. Chem.* **25**, 25 (1960).

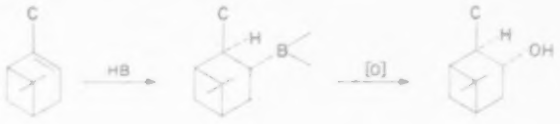
The hydroboration of norbornene proceeds to give *exo*-norborneol almost exclusively (35).



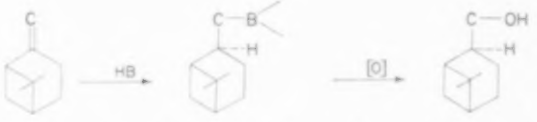
(35)

It appears, therefore, that hydroboration proceeds via a *cis* addition, preferentially from the less hindered side of the double bond.

This generalization is now supported by a considerable number of independent observations. Thus α-pinene is readily converted by this procedure into isopinocampheol (36),[23] and β-pinene into *cis*-myrtanol (37).[25]



(36)



(37)

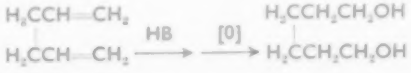
Similarly, the hydroboration of cholesterol produces cholestane-3β,6α-diol preferentially, clearly the result of a preferential *cis* addition from the less hindered under side of the molecule (38).[17]

(38)

This simple synthesis of stereochemically defined products should make the hydroboration reaction of especial value for the synthesis of steroid derivatives and related natural products,[11,17,18,26]

Dienes[27] *and acetylenes*[28]

Hydroboration provides a convenient synthetic route to diols. Thus 1,3-butadiene is transformed into 1,4-butanediol and 1,5-hexadiene is converted into 1,6-hexanediol (39).

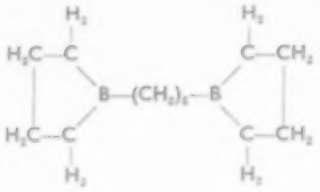


(39)

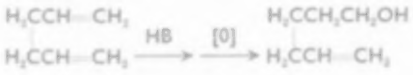
[23] Research in progress with M. V. Bhatt.
[26] P. Bruck, D. Thompson and S. Winstein, *Chem. & Ind.* 405 (1960).
[27] H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.* **81**, 5832 (1959).
[28] H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.* **81**, 1512 (1959).

The generality of this synthesis has been demonstrated for a considerable number of additional dienes.[29]

Köster has isolated the organoborane from butadiene and has assigned it a cyclic structure.[30]



The partial hydroboration of dienes provides a valuable synthetic route to the synthesis of unsaturated alcohols (40,[27] 41,[27] 42[24]).



(40)

(41)

(42)

The reagent, bis-3-methyl-2-butylborane, provides a convenient means to achieve the partial hydroboration of the less hindered double bond in a diene.[22] Thus, the more active exocyclic double bonds in vinylcyclohexene and D-limonene are readily hydrated without attack on the less active double bond in the ring (43, 44).

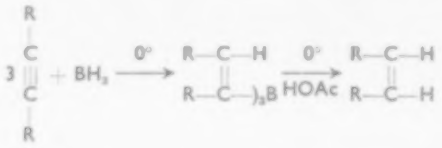
(43)

(44)

The hydroboration of internal acetylenes proceeds readily and can be controlled to give predominantly a single addition of a boron–hydrogen bond per acetylene

[29] K. A. Saegebarth, *J. Amer. Chem. Soc.* **82**, 2081 (1960).
[30] R. Köster, *Angew. Chem.* **71**, 520 (1959).

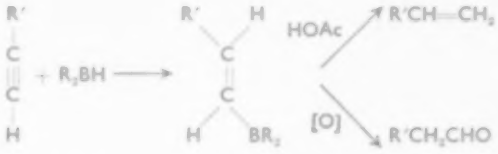
molecule. The resulting products are readily converted to the corresponding *cis* olefins in high purity by treatment at 0° with acetic acid (45).[28]



(45)

The corresponding reaction is less simple in the case of 1-alkynes, apparently proceeding predominantly to the dihydroboration stage. However, here also, the reagent bis-3-methyl-2-butylborane circumvents the difficulty and permits the formation of the monohydroborated product.

Treatment of this product with acetic acid yields the 1-alkene in 90 per cent yield (46) while oxidation of the organoborane forms the corresponding aldehyde in similar yield (47).



(46)

(47)

The dihydroboration of acetylenes appears to place two boron atoms on the same carbon atom. Oxidation of the products yields the ketone predominantly from an internal acetylene and the aldehyde from a terminal acetylene. The precise nature of these organoboranes is under investigation.

Oxidation of organoboranes

The lower alkylboranes are spontaneously inflammable in air, whereas tri-n-butylborane and the higher members react with oxygen, but do not inflame. Considerable study has been devoted to uncovering the precise course of the reaction with oxygen.[8,31,32] However, since air oxidation has not proven to be valuable in synthetic work, the results will not be discussed here.

On the other hand, the oxidation of organoboranes by alkaline hydrogen peroxide,[6–8] has proven to be of immense practical value in synthetic work. Accordingly, a detailed study of the reaction was undertaken.[33]

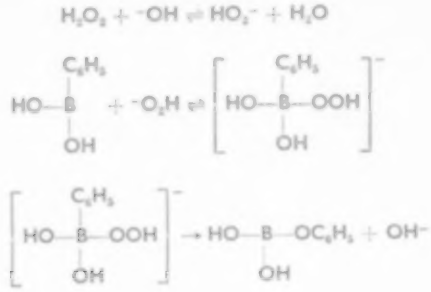
It was established that the oxidation of the organoborane is essentially quantitative at 25° in the usual hydroboration solvents—diglyme and tetrahydrofuran. Consequently, the oxidation can be carried out directly on the newly synthesized organoborane *in situ*, without isolation. In cases where the solvent is ethyl ether or a similar medium not miscible with water, the addition of ethanol as a co-solvent likewise results in essentially quantitative yields.

Wide variation in the structure of the olefin can be tolerated in this reaction. No instance has yet turned up of an organoborane which resists this oxidation under the usual mild conditions.

[31] R. C. Petry and F. H. Verhoek, *J. Amer. Chem. Soc.* **78**, 6416 (1956).
[32] A. G. Davies and R. B. Moodie, *Chem. & Ind.* 1622 (1959).
[33] H. C. Brown, C. Snyder, B. C. Subba Rao and G. Zweifel, manuscript in preparation.

Numerous substances, such as olefins, acetylenes, dienes, esters, ketones and nitriles, may be present in the reaction mixture without influencing the yield of oxidation product from the organoborane, or exhibiting any attack on themselves. This indicates that the reaction will be applicable not only to simple organoboranes, but also to their functional derivatives now readily available by the hydroboration of unsaturated compounds.

A detailed kinetic study of the reaction has not yet been reported. However, Kuivila *et al.* have examined the closely related reaction of benzeneboronic acid with hydrogen peroxide.[34] They propose the mechanism (48):



(48)

An identical mechanism, in three successive stages, is consistent with all of the available data for the oxidation with alkaline hydrogen peroxide.[17] In this mechanism the organic group shifts with its pair of electrons from boron to oxygen. This is consistent with the retention of configuration which is observed in the hydroboration–oxidation of cyclic olefins.

The direct oxidation of organoboranes to ketones with chromic acid has been accomplished.[35] Thus, a cyclic olefin such as cyclohexene, can be hydroborated and directly oxidized *in situ* with aqueous chromic acid to cyclohexanone in satisfactory yield (49).[36]

(49)

Protonolysis[37]

The trialkylboranes are remarkably stable toward hydrolysis with water. Even in the presence of strong mineral acids the hydrolysis is slow and incomplete. Thus the treatment of tributylborane with 48 per cent hydrobromic acid under reflux results in loss of but one of the three alkyl groups, with the formation of a quantitative yield of dibutylboronic acid.[38]

[34] H. G. Kuivila, *J. Amer. Chem. Soc.* **76**, 870 (1954); *Ibid.* **77**, 4014 (1955); H. G. Kuivila and R. A. Wiles, *Ibid.* **77**, 4830 (1955); H. G. Kuivila and A. G. Armour, *Ibid.* **79**, 5659 (1957).
[35] R. Pappo, *J. Amer. Chem. Soc.* **81**, 1010 (1959).
[36] Research in progress with C. P. Garg.
[37] H. C. Brown and K. J. Murray, *J. Amer. Chem. Soc.* **81**, 4108 (1959).
[38] J. R. Johnson, H. R. Snyder and M. G. Van Campen, Jr., *J. Amer. Chem. Soc.* **60**, 115 (1938).

It is quite remarkable that the organoboranes are far more susceptible to attack by carboxylic acids than by the mineral acids.

For example, under relatively mild conditions triethylborane reacts with acetic acid to form diethylboron acetate and ethane (50).[39]

$$(C_2H_5)_3B + CH_3CO_2H \xrightarrow{100^\circ} (C_2H_5)_2BOCOCH_3 + C_2H_6 \qquad (50)$$

A detailed study of the action of carboxylic acids on organoboranes has demonstrated that two of the three groups can be removed by excess dry acetic or propionic acid at room temperature, and all three groups can generally be removed by heating the organoborane in diglyme solution with a slight excess of the carboxylic acid for 2 to 3 hours.[37] (Propionic acid is preferred over acetic acid because of its lower volatility).

Consequently, hydroboration of olefins in diglyme, followed by addition of propionic acid and refluxing, provides a convenient non-catalytic procedure for the hydrogenation of double-bonds (51).

$$3RCH{=}CH_2 \xrightarrow{HB} (RCH_2CH_2)_3B \xrightarrow{C_2H_5CO_2H} 3RCH_2CH_3 \qquad (51)$$

Secondary alkyl groups undergo protonolysis less readily than primary. Consequently, in hydroborating internal olefins, it is preferable that the boron be transferred to the terminal position by heating under reflux prior to addition of the acid. (This isomerization of organoboranes is discussed later.)

It has been established that olefins containing relatively active sulfur, chlorine and nitrogen substituents undergo hydroboration readily. Consequently, hydroboration followed by protonolysis opens up the possibility of hydrogenating double bonds in molecules containing such labile groups. Indeed, the conversion of allylmethyl sulfide into n-propylmethyl sulfide by this method proceeds in good yield, whereas hydrogenation with the usual metal catalysts results in the loss of the thiomethyl group.[37]

As was indicated earlier, organoboranes of the vinyl type, readily obtained by the hydroboration of acetylenes, undergo protonolysis much more readily. These compounds undergo complete protonolysis with acetic acid in a matter of minutes at 0°, and the reaction provides a convenient means of converting acetylenes into *cis* olefins of high purity.[28]

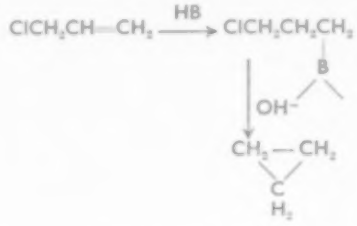
Mercuration. Grignard-like reactions

The ability of trialkylboranes to function as a Grignard reagent has as yet received little attention. Consequently, considerable interest attaches to the report by Honeycutt and Riddle that they have synthesized diethylmercury by treating mercuric oxide with triethylborane and sodium hydroxide in water at 75°. The reaction was fast, complete in 10 minutes, with a yield of 95 per cent based on the mercuric oxide.[40]

More recently these authors have demonstrated the synthesis of di-n-hexylmercury and of tetraethyllead by related procedures.[41]

[28] J. Goubeau, R. Epple, D. D. Ulmschneider and H. Lehmann, *Angew. Chem.* **67**, 710 (1955).
[40] J. B. Honeycutt, Jr. and J. M. Riddle, *J. Amer. Chem. Soc.* **81**, 2593 (1959).
[41] J. B. Honeycutt, Jr. and J. M. Riddle, *J. Amer. Chem. Soc.* **82**, 3051 (1960).

An unusually interesting Grignard-like reaction was discovered by Hawthorne and Dupont. They noted that treatment of the hydroboration product from allyl chloride with alkali brought about cyclization to form cyclopropane (52).[42]

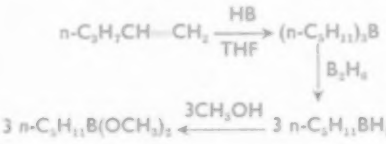


(52)

This reaction offers promise as a general synthesis of substituted cyclopropanes.[43]

Redistribution reactions

Equilibration of trialkylboranes with excess diborane provides a convenient route to the monoalkylboranes (or their dimers). These monoalkylboranes are readily alcoholyzed to the corresponding boronic esters or hydrolyzed to the boronic acid. Consequently, hydroboration provides a convenient route to these derivatives (53).[44]



(53)

By controlling the amount of excess diborane, it is possible to direct the equilibration reaction to the dialkylborane stage. Alternatively, addition of the olefin to excess diborane in tetrahydrofuran solution at 0° results in the formation of the dialkylborane in good yield. In this way hydroboration likewise provides convenient routes to the dialkylborinic acids and esters.[44]

Boron trichloride reacts rapidly with trialkylboranes at temperatures above 100° to give nearly quantitative yields of dialkylchloroboranes.[45,46] The reaction has been demonstrated for tri-n-butylborane, triisobutylborane, and tri-sec-butylborane, so that it is relatively insensitive to the structure of the alkyl group. At elevated temperatures the redistribution can be carried one step further—to the monoalkyldichloroboranes. These reactions provide an alternative route to the boronic and borinic acids and their derivatives.

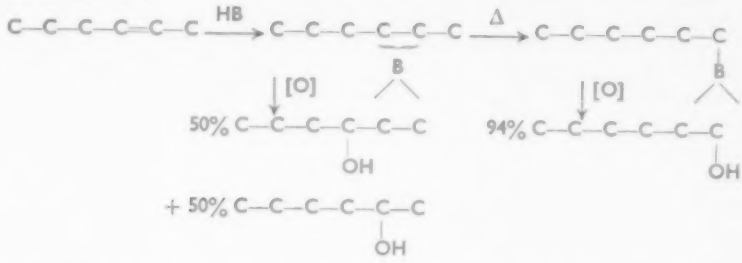
Isomerization of organoboranes[47]

At elevated temperatures secondary organoboranes are slowly isomerized into the primary derivatives. Thus, Hennion *et al.* observed that tri-sec-butylborane was transformed into tri-n-butylborane by heating at 200–215° for 48 hours.[48]

[42] M. F. Hawthorne and J. A. Dupont, *J. Amer. Chem. Soc.* **80**, 5830 (1958).
[43] M. F. Hawthorne, *J. Amer. Chem. Soc.* **82**, 1886 (1960).
[44] H. C. Brown, A. Tsukamoto and D. B. Bigley, *J. Amer. Chem. Soc.* **82**, 4703 (1960).
[45] V. W. Buls, O. L. Davis and R. I. Thomas, *J. Amer. Chem. Soc.* **79**, 337 (1957).
[46] P. A. McCusker, G. F. Hennion and E. C. Ashby, *J. Amer. Chem. Soc.* **79**, 5192 (1957).
[47] H. C. Brown and B. C. Subba Rao, *J. Org. Chem.* **22**, (1957); *J. Amer. Chem. Soc.* **81**, 6434 (1959).
[48] G. F. Hennion, P. A. McCusker, E. C. Ashby and A. J. Rutkowski, *J. Amer. Chem. Soc.* **79**, 5190 (1959).

The isomerization is far more rapid under hydroboration conditions.[47] Thus, tri-2-hexylborane is almost completely isomerized into tri-n-hexylborane in 1 hour at 160° in diglyme solution. It has been established that small quantities of excess diborane, produced in the hydroboration stage, markedly catalyze the isomerization and make possible the low-temperature reaction.[49]

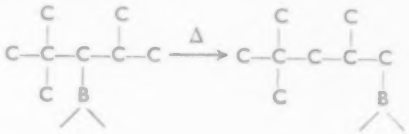
The isomerization reaction makes possible the synthesis of primary alcohols from internal olefins (54).



(54)

In this way it has been possible to transform a mixture of decenes containing no 1-decene into 1-decanol and a similar mixture of tetradecenes into 1-tetradecanol.

The boron atom not only moves readily down a long straight chain, but it exhibits no difficulty in moving past a single alkyl branch (55, 56).[47]



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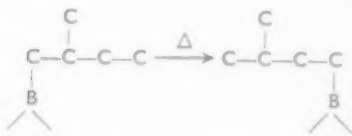
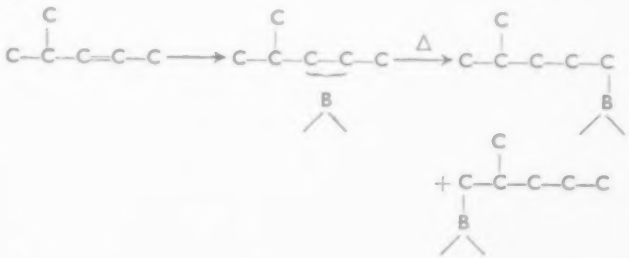


(56)

However, under these mild conditions the boron does not migrate past a double branch, (57, 58).



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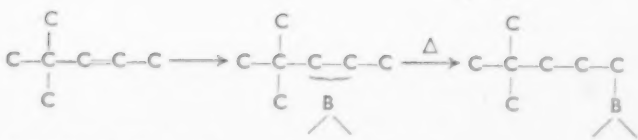
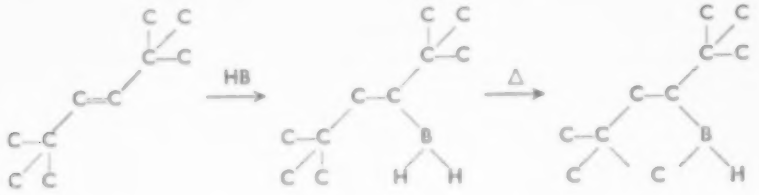


(58)

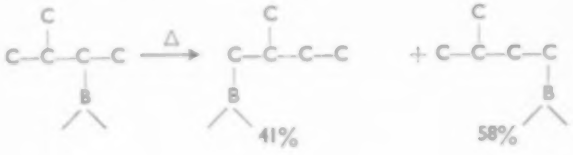
[49] Unpublished research with G. Zweifel.

Logan and Flautt attempted to examine the behaviour of a boron atom trapped between two quaternary carbon atoms. However, in this case a cyclization reaction occurred under relatively mild conditions (59).[20]

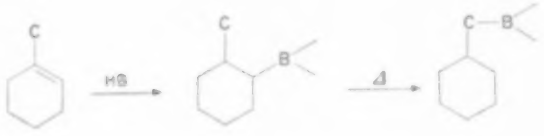


(59)

In the usual isomerization, the boron atom migrates preferentially to the least hindered position in the molecule (60, 61, 62).



(60)



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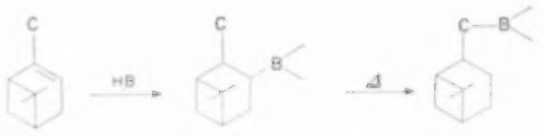
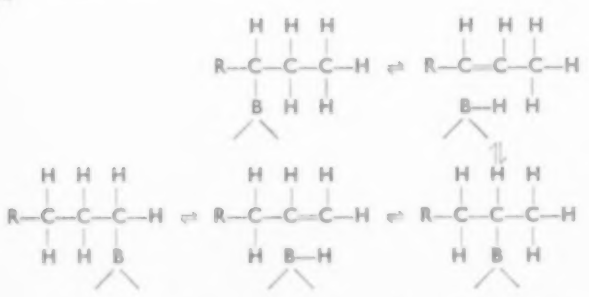


(62)

The isomerization of the boron atom from an internal position on a carbon chain to the terminal position can be formulated as a succession of eliminations and additions (63).[47]



(63)

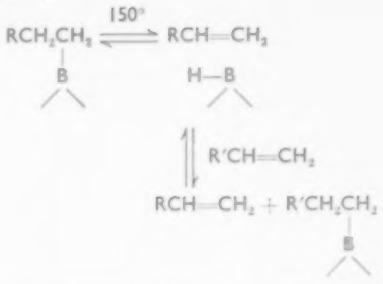
The preference of the boron for the terminal position is postulated to be the result of decreased steric interactions in that location. All of the available data for the

[20] H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.* **82**, 1504 (1960).

isomerization of organoboranes are consistent with this elimination–addition mechanism.

Displacement reactions[16,47,51]

It is a consequence of the mechanism outlined above for the isomerization of organoboranes that a high concentration of an olefin of similar or greater reactivity should result in the displacement of some or all of the olefin formed in the elimination stage. Ultimately there would result an equilibrium mixture of all of the possible organoboranes and the two olefins (64).



(64)

A large excess of the displacing olefin shifts the equilibrium far toward the formation of the new organoborane. Alternatively, in cases where the displacing olefin is less volatile than the product olefin produced from the organoborane, the reaction is conveniently completed by removing the more volatile olefin from the reaction mixture by distillation (65).

$$(RCH_2CH_2)_3B + 3R'CH{=}CH_2 \xrightarrow{150^\circ} 3RCH{=}CH_2 + (R'CH_2CH_2)_3B \qquad (65)$$

This reaction has been utilized by Köster as a convenient synthesis of organoboranes.[16] Commonly triisobutylborane, readily available from the reaction of triisobutylaluminum with methyl borate, was heated with various olefins to displace isobutylene and to form the corresponding organoborane. In this way he has synthesized numerous organoboranes, such as tri-n-decylborane (66), tricyclohexylborane (67) and tri-(2-phenylpropyl)-borane (68).

$$3\ n\text{-}C_8H_{17}CH{=}CH_2 + [(CH_3)_2CHCH_2]_3B \longrightarrow (n\text{-}C_8H_{17}CH_2CH_2)_3B + 3(CH_3)_2C{=}CH_2 \qquad (66)$$

$$3\ C_6H_{10} + [(CH_3)_2CHCH_2]_3B \longrightarrow (C_6H_{11})_3B + 3\ (CH_3)_2C{=}CH_2 \qquad (67)$$

$$3\ C_6H_5C(CH_3){=}CH_2 + [(CH_3)_2CHCH_2]_3B \longrightarrow [C_6H_5CH(CH_3)CH_2]_3B + 3\ (CH_3)_2C{=}CH_2 \qquad (68)$$

The emphasis has been different in our studies. Hydroboration provides such a convenient route to the organoboranes that the displacement reaction has been explored primarily as a new type of elimination reaction which permits the preparation of olefins under relatively moderate reaction conditions with very mild reagents.

The utility of this reaction to produce pure olefins of representative structural types was tested as follows. The olefins were hydroborated to form the corresponding trialkylboranes. 1-Decene was added to the reaction mixture and the olefin product was distilled out of the refluxing reaction mixture. In each case the purity of the product was established by vapor phase chromatography. The yields averaged 80 ± 10 per cent.

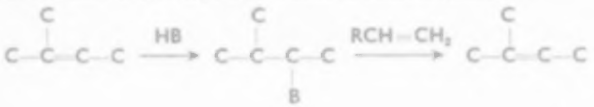
[51] H. C. Brown and M. V. Bhatt, *J. Amer. Chem. Soc.* **82**, 2074 (1960).

Terminal olefins, such as 1-pentene, 1-hexene, 3-methyl-1-butene and 3-ethyl-1-pentene required approximately 6–8 hours for completion. The products were 90–96 per cent pure 1-olefins with 5–10 per cent of the 2-olefin. The 2-olefin was contained in the initial fractions of the distillation. Evidently, this side-product arises from the 6–7 per cent of the 2-alkylboron derivative formed in the hydroboration of a terminal olefin and this structure must undergo displacement more readily than the 1-alkylborane present.

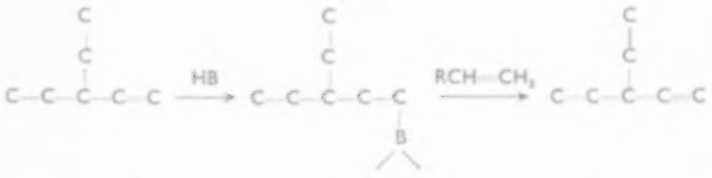
Terminal olefins containing two alkyl substituents, such as 2-methyl-1-butene and 2,4,4-trimethyl-1-pentene, are displaced more readily, with 2 to 4 hours being adequate for completion of the reaction. In these cases the olefin products exhibit a purity of 98–99 per cent.

Finally, internal olefins, such as 2-methyl-2-butene (69), 3-ethyl-2-pentene (70), 2,4,4-trimethyl-2-pentene, cyclopentene and cyclohexene, undergo displacement to produce the corresponding olefin in high purity.

Even such labile structures, such as methylenecyclohexene (71) and β-pinene (72), can be hydroborated and then displaced without rearrangement.



(69)

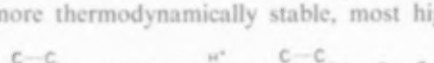


(70)

(71)

(72)

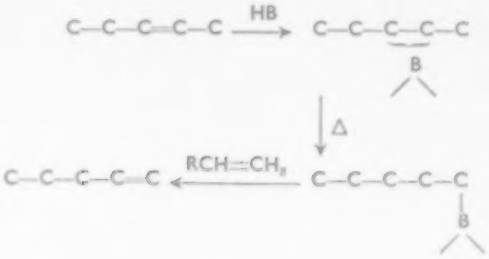
The usual acid-catalyzed isomerization of terminal olefins results in a preferential migration of the double bond into the chain or ring, with the final product being predominantly the more thermodynamically stable, most highly substituted olefin (73, 74).



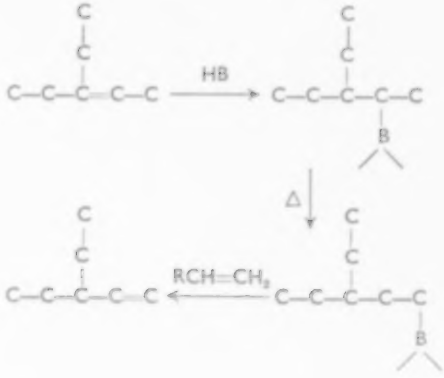
(73)

(74)

Hydroboration, isomerization of the organoborane, followed by displacement, provides a convenient synthetic route for the reverse transformation (75, 76, 77).



(75)



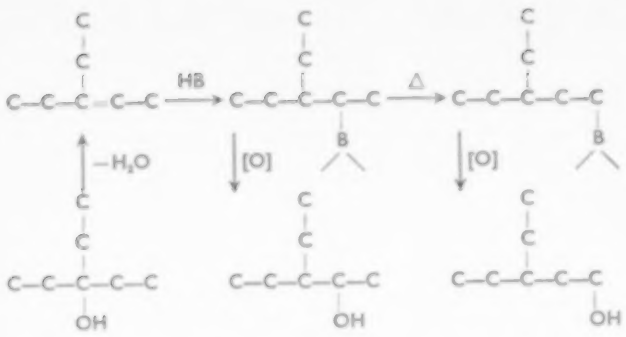
(76)

(77)

This contra-thermodynamic isomerization promises to be an exceedingly valuable synthetic procedure.

Conclusion

The remarkable versatility of the hydroboration reaction is illustrated by the following transformations, all of which proceed readily in yields in the neighborhood of 90 per cent (78).



(78)

The first report of a simple laboratory procedure for the hydroboration of olefins dates back only to late 1956.[6] Since that time the literature dealing with this subject has grown enormously, and it was not possible within the limits of this discussion to present a complete review. It is hoped that any injustices resulting from these limitations may largely be remedied in a more detailed review of this topic now under preparation.

Finally, it should be pointed out that even though developments have been rapid they show no signs of abating.[52,53] We can be confident that new, important synthetic procedures based on the hydroboration reaction will be forthcoming. The hydroboration reaction promises to become one of the major synthetic tools at the disposal of the organic chemist.

Acknowledgements—Finally, it is a pleasure to acknowledge that these studies were greatly facilitated by grants from Parke, Davis and Co., The Upjohn Co., American Cyanamid Co., and the Ethyl Corporation.

[52] K. A. Saegebarth, *J. Amer. Chem. Soc.* **82**, 2081 (1960).
[53] R. Köster and G. Rotermund, *Angew. Chem.* **72**, 138, 563 (1960).

Tetrahedron, 1961, Vol. 12, pp. 139 to 145. Pergamon Press, Inc. Printed in Northern Ireland

VOL. 12 1961

THE CHEMISTRY OF MOULD METABOLITES—IV

REDUCTIVE ACETYLATION AND REOXIDATION OF SOME PHENOXAZIN-3-ONES

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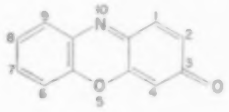
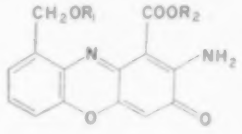
(*Received* 20 *September* 1960)

Abstract—The reductive acetylation of some substituted phenoxazin-3-ones including cinnabarinic acid is described, the products being characterized by infra-red spectroscopy. Additional support is provided for the structures assigned to the reduced acetylated derivatives of cinnabarin and its methyl ester. Nitrous acid has general application as an oxidant for the conversion of phenoxazines into phenoxazin-3-ones.

RECENT investigations have shown the existence of a new class of organic pigments in Nature represented by the ommochromes,[1] the actinomycins[2,3] and cinnabarin.[4,5] The presence of the phenoxazone chromophore (I) in these pigments has revived interest in phenoxazine chemistry, a study that has lain dormant for the last half century. The reductive acetylation of various phenoxazin-3-ones, and their subsequent reoxidation with nitrous acid has now been further investigated. These reactions have been employed in the characterization of cinnabarin and its derivatives.[4–6]

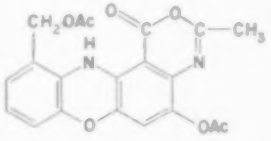


I

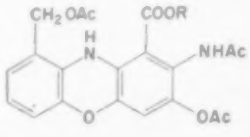


II

Reductive acetylation of cinnabarin (II, $R_1 = R_2 = H$) yielded triacetylanhydrodihydrocinnabarin (III)[4–6] whilst a triacetyldihydro derivative (IV, R = H) was obtained as a by-product.[5] Similarly, methyl cinnabarin (II, $R_1 = H$, $R_2 = CH_3$) gave methyl triacetyldihydrocinnabarin (IV, $R = CH_3$).[4,6] Since O-acetylcinnabarin (II, $R_1 = Ac$, $R_2 = H$) and methyl O-acetylcinnabarin (II, $R_1 = Ac$, $R_2 = CH_3$) can



III



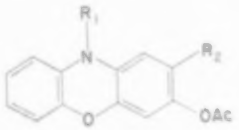
IV

[*] Part III, G. W. K. Cavill, P. S. Clezy, J. R. Tetaz and R. L. Werner, *Tetrahedron* **5**, 275 (1959).

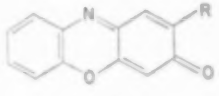
[1] A. Butenandt, V. Schieldt, E. Bickert and R. J. T. Cromartie, *Liebigs Ann.* **590**, 75 (1955).
[2] H. Brockmann and H. Muxfeldt, *Angew. Chem.* **68**, 69 (1956).
[3] S. J. Angyal, E. Bullock, W. G. Hangar, W. C. Howell and A. W. Johnson, *J. Chem. Soc.* 1592 (1957).
[4] G. W. K. Cavill, P. S. Clezy, J. R. Tetaz and R. L. Werner, *Tetrahedron* **5**, 275 (1959).
[5] J. Gripenberg, *Acta Chem. Scand.* **12**, 603 (1958).
[6] G. W. K. Cavill, B. J. Ralph, J. R. Tetaz and R. L. Werner, *J. Chem. Soc.* 525 (1953).

also be converted into III and IV (R = CH_3) respectively, one acetyl group was accommodated on the primary alcoholic group at position 9.[4,7] The second acetyl group was placed at position 3, thereby stabilizing the reduced products. The third was placed on the 2-amino substituent. The "anhydro" derivative (III) was formulated as an oxazinone, involving the cyclization of the 1-carboxy and 2-acetylamino substituents, and the absence of such a derivative from the products of reductive acetylation of methyl cinnabarin supports this formulation.[4,5]

In the present studies, the reductive acetylation of some model phenoxazin-3-ones gives two series of phenoxazine derivatives, in which, the degree of acetylation depends upon the reaction conditions. Under mild conditions, 3-acetoxyphenoxazines are obtained, whilst more vigorous conditions are required to achieve acetylation of the ring nitrogen atom. Mild reductive acetylation of phenoxazin-3-one (I) gives a monoacetyl derivative, formulated as 3-acetoxyphenoxazine (V, $R_1 = R_2 = H$) on the basis of its absorption at 3336 cm^{-1} (NH, cf. phenoxazine 3386 cm^{-1}) and at 1750 cm^{-1} (aromatic acetate, cf. 3,5-dimethoxy-2-diacetylaminophenylacetate 1763 cm^{-1}).[8,*] The lowered NH frequency of 3-acetoxyphenoxazine is presumably due to hydrogen bonding with the ester group.[9] More vigorous reductive acetylation of phenoxazin-3-one gives a diacetyl derivative, transparent in the 3μ region of the spectrum, but showing absorption at 1756 cm^{-1} (aromatic acetate) and 1687 cm^{-1} (N-acetyl, cf. 10-acetylphenoxazine 1672 cm^{-1}). The diacetyl derivative is then formulated as 3-acetoxy-10-acetylphenoxazine (V, R_1 = Ac, R_2 = H). Comparably, 2-methoxy-3-acetoxyphenoxazine (V, R_1 = H, R_2 = OCH_3) and 2-methoxy-3-acetoxy-10-acetylphenoxazine (V, R_1 = Ac, R_2 = OCH_3) have been obtained from 2-methoxyphenoxazin-3-one (VI, R = OCH_3).



V



VI

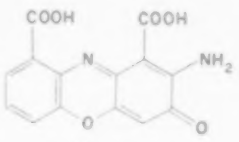
The pattern is complicated by the presence of the substituent groups in 2-hydroxy and 2-aminophenoxazin-3-one (VI, R = OH and R = NH_2, respectively). Vigorous reductive acetylation of 2-hydroxyphenoxazin-3-one produced a triacetate showing bands at 1775 cm^{-1} (aromatic acetate) and 1694 cm^{-1} (N-acetyl), which are consistent with structure (V, R_1 = Ac, R_2 = OAc) for this compound. The diacetate obtained under milder conditions, exhibits absorptions at 3342 cm^{-1} (NH) and 1767, 1749 cm^{-1} (aromatic acetate). The lower of these carbonyl absorptions is assigned to a hydrogen bonded ester carbonyl group. Mild reductive acetylation of 2-aminophenoxazin-3-one yields a diacetate, with absorptions at 3302 cm^{-1} (NH), 1730 cm^{-1} (aromatic acetate) and 1672 cm^{-1} (N-acetyl). Reference to the previous model compounds shows clearly that vigorous conditions are necessary for the acetylation of the bridge NH group, so that the latter frequency (1672 cm^{-1}) is assigned to an acetylamino group in position 2.

* Infra-red absorption spectra are reported for "Nujol" mulls. The majority of these acetylated product are insufficiently soluble for examination in solution.

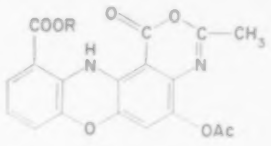
[7] J. Gripenberg, *Proc. Chem. Soc.* 233 (1957).
[8] J. F. Grove, P. W. Jeffs and D. W. Rustidge, *J. Chem. Soc.* 1956 (1956).
[9] R. E. Richards and H. W. Thompson, *J. Chem. Soc.* 1248 (1947).

Hence this diacetate is formulated as 2-acetylamino-3-acetoxyphenoxazine (V, $R_1 = H$, $R_2 = NHAc$). Two products were obtained by vigorous reductive acetylation of 2-aminophenoxazin-3-one, a triacetate (V, $R_1 = H$, $R_2 = NAc_2$) showing absorptions at 3340 cm^{-1} (NH), 1769 cm^{-1} (aromatic acetate), 1710, 1701 cm^{-1} (diacetylamine[8,10]), and a tetraacetate (V, $R_1 = Ac$, $R_2 = NAc_2$)[1] with absorptions at 1677 cm^{-1} (N-acetyl), 1770 cm^{-1} (aromatic acetate), and 1723, 1710 cm^{-1} (diacetylamine). These assignments are in accord with the formulations given above.

In contrast to these systems, cinnabarinic acid (VII) on reductive acetylation yields only one product, a diacetate, which has carbonyl bands at 1760 cm^{-1} and 1743 cm^{-1}



VII

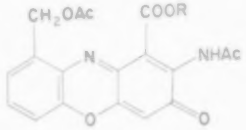


VIII

(aromatic acetate and oxazinone respectively, cf. triacetylanhydrodihydrocinnabarin 1769 and 1736 cm^{-1}). A third carbonyl band at 1672 cm^{-1} is assigned to the hydrogen bonded carbonyl group, and the absorption at 3240 cm^{-1} is that of the N—H group of the phenoxazine ring. Diacetylanhydrodihydrocinnabarinic acid is thus formulated as (VIII, R = H), and methylation of this compound with diazomethane, yields a monomethyl ester (VIII, $R = CH_3$) further supporting the presence of the oxazinone system.

The above results verify the structures III and IV, ($R = CH_3$) proposed independently[4,5] for the reduced acetylated derivatives of cinnabarin and of methyl cinnabarin. Moreover, the isolation of only one derivative from the reductive acetylation of cinnabarinic acid supports the hypothesis[4,5] that acetylation of the ring nitrogen atom is prevented by steric effects of the large groups at positions 1 and 9.

Previous papers[4,11] from this laboratory have described the use of nitrous acid for the oxidation of triacetylanhydrodihydrocinnabarin (III) to O, N-diacetylcinnabarin (IX, R = H), and for the oxidation of methyl triacetyldihydrocinnabarin (IV, $R = CH_3$) to methyl O-N-diacetylcinnabarin (IX, $R = CH_3$).



IX

This oxidation process is now shown to have general application. Phenoxazine is converted into phenoxazin-3-one (I), at 5°, but more vigorous conditions (60° for 5 mins) are needed to obtain the same product from 10-acetylphenoxazine. 3-Acetoxyphenoxazine (V, $R_1 = R_2 = H$) and 3-acetoxy-10-acetylphenoxazine (V, $R_1 = Ac$, $R_2 = H$) also yield phenoxazin-3-one, when treated with nitrous acid at 5°. Similarly, 2-acetylamino-, 2-diacetylamino-, and 10-acetyl-2-diacetylamino-3-acetoxyphenoxazine (V, $R_1 = H$, $R_2 = NHAc$; $R_1 = H$, $R_2 = NAc_2$; $R_1 = Ac$, $R_2 = NAc_2$

[10] R. A. Abramovitch, *J. Chem. Soc.* 1413 (1957).
[11] G. W. K. Cavill, P. S. Clezy and J. R. Tetaz, *J. Chem. Soc.* 2646 (1957).

respectively) are converted into 2-acetylaminophenoxazin-3-one (VI, R = NHAc); whilst 2,3 diacetoxyphenoxazine (V, R_1 = H, R_2 = OAc) and 2,3-diacetoxy-10-acetylphenoxazine (V, R_1 = Ac, R_2 = OAc) yield 2-acetoxyphenoxazin-3-one (VI, R = OAc). Finally, 2-methoxy-3-acetoxyphenoxazine (V, R_1 = H, R_2 = OCH_3) and its 10-acetyl derivative, require a more vigorous oxidation to give 2-methoxyphenoxazin-3-one (VI, R = OCH_3).

The generality of the oxidation process described above, confirms the phenoxazin-3-one structures (IX, R = H and R = CH_3) previously assigned[4] to the products obtained by the action of nitrous acid on triacetylanhydrodihydrocinnabarin (III) and methyl triacetyldihydrocinnabarin (IV, R = CH_3).

EXPERIMENTAL

Light petroleum has b.p. 60–80°. Alumina refers to aluminium oxide, grade H, (Peter Spence), neutralized by the method given previously.[11] Carbon, hydrogen and nitrogen analyses are by Dr. E. Challen of this University, additional analyses are by C.S.I.R.O. Microanalytical Laboratory (Melbourne). Wenzel's dilute sulphuric acid was used for hydrolysis during acetyl determinations. The infra-red absorption spectra, determined by Mr. I. H. Reece, were measured in "Nujol", and the bands in the 3μ and 6μ regions are recorded below. Mr. D. Weedon determinated the ultra-violet absorption spectra using 95% ethanol as solvent. All m.p.s are uncorrected.

3-*Acetoxyphenoxazine*. Phenoxazin-3-one (750 mg), prepared after Kehrmann and Saager,[12] and purified by alumina chromatography and sublimation *in vacuo*, in acetic anhydride (20 ml) and pyridine (1 ml) was shaken with an excess of zinc dust at room temp for 15 min and then heated at at 100° for 3 min. The pale yellow solution, separated from excess zinc by decantation, was poured onto ice when a white solid precipitated (300 mg). This solid was dissolved in chloroform, the solution washed with saturated aqueous sodium hydrogen carbonate, and water, and then dried (Na_2SO_4). Evaporation of the solvent gave a crystalline residue, which after recrystallization from benzene–light petroleum gave 3-*acetoxyphenoxazine*, as colourless plates, m.p. 144–145°. ν_{max} 3336 (m), 1750 (s) cm^{-1}. (Found: C, 70·1; H, 4·3; N, 5·75; Ac, 18·4%. $C_{14}H_{11}O_3N$ requires: C, 70·0; H, 4·2; N, 5·8; Ac, 17·9%).

10-*Acetyl*-3-*acetoxyphenoxazine*. Phenoxazin-3-one (500 mg), in acetic anhydride (30 ml) and pyridine (2 ml) was shaken with zinc dust (4 g) at room temp for 10 min. The pale yellow reaction mixture, after heating under reflux for 10 min, was worked up as above.

10-*Acetyl*-3-*acetoxyphenoxazine* (250 mg) was obtained from benzene–light petroleum as colourless needles, m.p. 124·5—126°. ν_{max} 1756 (s), 1687 (s) cm^{-1}. (Found: C, 67·6; H, 4·35; N, 5·0; Ac, 30·0%. $C_{16}H_{13}O_4N$ requires: C, 67·8; H, 4·6; N, 4·95; 2Ac, 30·4%).

2-*Hydroxyphenoxazin*-3-*one* (modification of Diepolder's method).[13] A mixture of 2-aminophenol (6 g), ferric chloride hexahydrate (40 g) and hydrochloric acid (10 N; 350 ml) was heated under reflux for 6 hr. The deep brown solution was diluted with water (700 ml), extracted with chloroform (16 × 100 ml) and the latter extract shaken with aqueous sodium carbonate (5%; 6 × 200 ml). The green fluorescent chloroform solution was rejected. The deep red alkaline solution was acidified to give a yellow precipitate (2 g) which was purified by vacuum sublimation (170–200°/2 mm), to give 2-hydroxyphenoxazin-3-one as a bright orange solid, m.p. 264° (decomp). Diepolder[13] reports m.p. 278° (decomp). (Found: C, 67·5; H, 3·4; N, 6·5%. Calc. for $C_{12}H_7O_3N$: C, 67·4, H, 3·3; N, 6·6%).

2,3-*Diacetoxyphenoxazine*. 2-Hydroxyphenoxazin-3-one (500 mg), in acetic anhydride (22 ml) and pyridine (1 ml) was heated under reflux for 3 min. When cool, the red solution was shaken with zinc dust (2 g) at room temp for 10 min, and then heated at 100° for 3 min. By the usual procedure, 2,3-diacetoxyphenoxazine (650 mg) was obtained as colourless plates, m.p. 145-146° from benzene–light petroleum. ν_{max} 3342 (w), 1767 (s), 1749 (s) cm^{-1}. (Found: C, 64·5; H, 4·4; N, 4·7; Ac, 28·0%. $C_{16}H_{13}O_5N$ requires: C, 64·2; H, 4·4; N, 4·7; 2Ac, 28·8%).

10-*Acetyl*-2,3-*diacetoxyphenoxazine*. (a) 2-Hydroxyphenoxazin-3-one (150 mg), in acetic anhydride (6 ml) and pyridine (3 drops) was heated under reflux for 3 min. The red solution, after

[12] F. Kehrmann and A. Saager, *Ber. Dtsch. Chem. Ges.* **35**, 341 (1902).
[13] E. Diepolder, *Ber. Dtsch. Chem. Ges.* **35**, 2816 (1902).

cooling, was shaken with zinc dust (200 mg) at room temp for 10 min. The resultant colourless solution was heated under reflux (1 hr) whence 10-*acetyl*-2-3-*diacetoxyphenoxazine* (120 mg) was finally obtained, as colourless plates, m.p. 142·5–143°, from benzene–light petroleum, depressed to 114° on admixture with 2,3-diacetoxyphenoxazine. ν_{max} 1775 (s) 1694 (s) cm^{-1} (Found: C, 63·0; H, 4·15; N, 4·55; Ac, 36·2%. $C_{18}H_{15}O_6N$ requires: C, 63·35; H, 4·4; N, 4·1; 3Ac, 37·7%).

(b) 2,3-Diacetoxyphenoxazine (450 mg) in acetic anhydride (15 ml) and pyridine (0·5 ml) was heated under reflux for 30 min. By the usual procedure, 10-*acetyl*-2,3-*diacetoxyphenoxazine* (300 mg) was obtained as colourless plates m.p. 142·5–143° from benzene–light petroleum. (Found: C, 63·6; H, 4·4; N, 4·4%. $C_{18}H_{15}O_6N$ requires: C, 63·35; H, 4·4; N, 4·1%).

2-*Methoxyphenoxazin*-3-*one*. 2-Hydroxyphenoxazin-3-one (500 mg) and anhydrous potassium carbonate (13·4 g) were suspended in dry acetone (500 ml) containing methyl iodide (10 g). The mixture was heated under reflux for 5 hr when methyl iodide (10 g) was added, and the heating continued (5 hr). The potassium carbonate was removed by filtration and the filtrate reduced in volume (100 ml) *in vacuo*, whereupon 2-*methoxyphenoxazin*-3-*one* (280 mg) precipitated. A further quantity (50 mg) was obtained by alumina chromatography of the residue obtained by complete removal of the solvent. Purification, by sublimation (180–190°/1·0 mm), gave 2-methoxyphenoxazin-3-one as a pale yellow solid, m.p. 255° (decomp). λ_{max} 222, 395 mμ (ε, 23·7 × 10³, 18·1 × 10³). (Found: C, 68·5; H, 3·8; N, 5·8% $C_{13}H_9O_3N$ requires: C, 68·7; H, 4·0; N, 6·2%).

2-*Methoxy*-3-*acetoxyphenoxazine*. 2-Methoxyphenoxazin-3-one (150 mg), in acetic anhydride (5 ml) and pyridine (2 drops) was shaken with zinc dust (150 mg) at room temp for 15 min. The colourless solution, separated from the excess zinc by decantation, was poured into ice, and the resultant solid was purified in the usual way. 2-Methoxy-3-acetoxyphenoxazine (150 mg) was obtained from benzene–light petroleum as colourless needles, m.p. 172–174°. ν_{max} 3336 (m), 1756 (s) cm^{-1}. (Found: C, 66·65; H, 5·0; N, 5·1; Ac, 14·3%. $C_{15}H_{13}O_4N$ requires: C, 66·4; H, 4·8; N, 5·2; Ac, 15·85%).

10-*Acetyl*-2-*methoxy*-3-*acetoxyphenoxazine*. 2-Methoxyphenoxazin-3-one (300 mg), in acetic anhydride (12 ml) and pyridine (1 ml) was shaken with zinc dust (3 g) at room temp for 10 min, after which the colourless solution was heated under reflux for 10 min. 10-*Acetyl*-2-*methoxy*-3-*acetoxyphenoxazine* (400 mg) was obtained from aqueous alcohol as colourless needles, m.p. 148–149°. ν_{max} 1755 (s), 1681 (s) cm^{-1}. (Found: C, 65·4; H, 4·9; N, 4·4; Ac, 25·3%. $C_{17}H_{13}O_5N$ requires: C, 65·2; H, 4·8; N, 4·5; 2Ac, 27·1%).

2-*Aminophenoxazin*-3-*one* (after Fischer and Jonas).[14] 2-Aminophenol (5 g) in chloroform (300 ml), was treated at 60° with yellow mercuric oxide (15 g) added over 15 min, the mixture being well stirred. Finally, the mixture was heated under reflux for 10 min, the deep red solution filtered and the filtrate concentrated *in vacuo* (50 ml). 2-Aminophenoxazin-3-one (4·7 g) which was obtained in a crystalline state from the concentrate, was further purified by recrystallization from benzene, to give deep purple plates, m.p. 256–257° (decomp) Fischer and Jonas[14] report m.p. 249° (decomp). (Found: C, 68·0; H, 3·6; N, 13·05%. Calc. for $C_{12}H_8O_2N_2$: C, 67·95; H, 3·8; N, 13·2%).

2-*Acetylamino*-3-*acetoxyphenoxazine*. 2-Aminophenoxazin-3-one (1 g), in acetic anhydride (43 ml), and pyridine (2 ml), was shaken with zinc dust (4 g) at room temp for 1½ hr. The colourless reaction mixture was then heated at 100° for 5 min. The usual working up procedure gave 2-*acetylamino*-3-*acetoxyphenoxazine* (900 mg) as colourless needles m.p. 220° from chloroform–benzene. ν_{max} 3302 (s), 1730 (s), 1675 (s) cm^{-1}. (Found: C, 64·3; H, 4·3; N, 9·1; Ac, 27·5%. $C_{16}H_{14}O_4N_2$ requires: C, 64·4; H, 4·7; N, 9·4; 2Ac, 28·9%).

10-*Acetyl*-2-*diacetylamino*-3-*acetoxyphenoxazine*. (a) 2-Aminophenoxazin-3-one (1 g), in acetic anhydride (43 ml) and pyridine (2 ml) was shaken with zinc dust (4 g) at room temp for 10 min, and the colourless reaction mixture then heated under reflux for 10 min. Following the usual procedure, the reduced acetylated product was obtained as a colourless solid, further resolved on recrystallization from benzene. The more soluble fraction, when recrystallized from benzene–light petroleum gave 10-acetyl-2-diacetylamino-3-acetoxyphenoxazine (600 mg) as heavy colourless plates, m.p. 181–182°. Cavill *et al*[4] reports m.p. 184–185°. ν_{max} 1677 (m), 1710 (s), 1723 (s), 1770 (s) cm^{-1}. (Found: C, 62·8; H, 4·6; N, 7·2; Ac, 45·1%). Calc. for $C_{20}H_{18}O_6N_2$: C, 62·75; H, 4·75; N, 7·3; 4Ac, 45·1%).

The less soluble product gave 2-*diacetylamino*-3-*acetoxyphenoxazine* (150 mg) further purified by

[14] O. Fischer and O. Jonas, *Ber. Dtsch. Chem. Ges.* **27**, 2782 (1894).

recrystallization from benzene–light petroleum as fine colourless needles m.p. 195–196°. ν_{max} 3340 (m), 1769 (s), 1710 (s), 1701 (s) cm^{-1}. (Found: C, 63·9; H, 4·4; N, 8·0; Ac, 37·4%. $C_{18}H_{16}O_5N_2$ requires: C, 63·5; H, 4·75; N, 8·2; 3Ac, 38·0%).

(b) 2-Acetylamino-3-acetoxyphenoxazine (60 mg), in acetic anhydride (5 ml) and pyridine (3 drops), was heated under reflux for 10 min, to yield 10-acetyl-2-diacetylamino-3-acetoxyphenoxazine (60 mg), which was isolated as colourless plates from benzene–light petroleum, m.p. and mixed m.p. with an authentic specimen, 179–180°. (Found: C, 63·1; H, 4·6; N, 7·4%. Calc. for $C_{20}H_{18}O_6N_2$: C, 62·75, H, 4·75; N, 7·3%).

(c) 2-Diacetylamino-3-acetoxyphenoxazine (70 mg), in acetic anhydride (6 ml) and pyridine (0·5 ml) was heated under reflux for 15 min. 10-Acetyl-2-diacetylamino-3-acetoxyphenoxazine (80 mg) was obtained as colourless plates, m.p. and mixed m.p. 181–182°, from benzene–light petroleum. (Found: C, 63·1; H, 4·8; N, 7·2%. Calc. for $C_{22}H_{18}O_6N_2$: C, 62·75; H, 4·75; N, 7·3%).

Diacetylanhydrodihydrocinnabarinic acid. Cinnabarinic acid[15] (175 mg), in acetic anhydride (10 ml) and pyridine (0·5 ml) was shaken with zinc dust (500 mg) at room temp for 5 min, and then heated at 100° for 5 min. *Diacetylanhydrodihydrocinnabarinic acid* (170 mg) was obtained as yellow needles, m.p. > 300° (decomp), from dioxan. λ_{max} 228, 245, 427–434 mμ (ε, 30·2 × 10^3, 22·8 × 10^3 12·2 × 10^3). ν_{max} 3240 (w), 1677 (s) 1743 (s), 1760 (s) cm^{-1}. (Found: C, 58·8; H, 3·4; N, 7·8; Ac, 20·8%. $C_{18}H_{12}O_7N_2$ requires C, 58·7; H, 3·3; N, 7·6; 2Ac, 23·4%). The identical product was obtained when cinnabarinic acid was reductively acetylated by heating under reflux for 10 min.

Diacetylanhydrodihydrocinnabarinic acid monomethyl ester. Diazomethane (2·3 g in 100 ml ether) was added to a suspension of diacetylanhydrodihydrocinnabarinic acid (160 mg) in ether (1 l.), and the mixture allowed to stand at 5° for 24 hr, then at room temp overnight. Dilute N acetic acid (7 ml) was added to destroy excess diazomethane, and the ethereal solution evaporated to dryness. Repeated recrystallization of the residue from benzene–light petroleum gave *diacetylanhydrodihydrocinnabarinic acid monomethyl ester* (40 mg) as yellow needles, m.p. 255–259° (Found: C, 60·2; H, 4·1; N, 7·2; Ac, 17·8%. $C_{19}H_{14}O_7N_2$ requires: C, 59·8; H, 3·7; N, 7·3; Ac, 22·5%).

Oxidation of phenoxazine. Phenoxazine (100 mg) in ethanol (95%; 5 ml) and 10N HCl (1 ml) was treated at 5° with aqueous sodium nitrite (30%; 2 ml). The colour of the reaction solution changed from red to dark blue and warming to 60° affected no change. After standing for 3 days at room temp the green reaction solution was extracted with chloroform (2 × 20 ml), the organic phase washed with saturated aqueous sodium hydrogen carbonate and water, and dried (Na_2SO_4). Removal of the solvent gave an orange solid (50 mg) which was purified by alumina chromatography, and sublimation (140–160°/1 mm) to give phenoxazin-3-one, m.p. 205–207° (decomp), undepressed on admixture with an authentic specimen. λ_{max} 243, 347, 447 mμ (ε, 17·6 × 10^3, 12·4 × 10^3, 11·1 × 10^3). (Found: C, 73·6; H, 3·8; N, 7·2%. Calc. for $C_{12}H_7O_2N$: C, 73·1; H, 3·6; N, 7·1%.)

Oxidation of 10-acetylphenoxazine. 10-Acetylphenoxazine (30 mg) dissolved in ethanol (95% 10 ml) and 10N HCl (3 ml) was treated at 5° with aqueous sodium nitrite solution (30%; 5 ml). No visible reaction was evident. The temp was then raised to 60° for 5 min, brown fumes were evolved and the solution became deep orange. After allowing the reaction mixture to stand at room temp; for 1 day, it was extracted with chloroform and worked up by the method outlined for the previous oxidation. Phenoxazin-3-one (5 mg) was isolated after vacuum sublimation, m.p. and mixed m.p. 208–209° (decomp). λ_{max} 245, 348, 447 mμ (ε, 18·5 × 10^3, 13·3 × 10^3, 11·3 × 10^3).

Oxidation of 3-acetoxyphenoxazine. 3-Acetoxyphenoxazine (100 mg), in ethanol (95%; 5 ml) and 10N HCl (1 ml) was treated at 5° with aqueous sodium nitrite solution (30%; 3 ml) for 3 days. By the above procedure phenoxazin-3-one (80 mg) was obtained after vacuum sublimation (140–160°/1 mm), m.p. and mixed m.p. 205–206° (decomp). λ_{max} 245, 348, 447 mμ (ε, 16·5 × 10^3, 12·1 × 10^3, 11·1 × 10^3). (Found: C, 72·8; H, 3·55, N, 7·3%. Calc. for $C_{12}H_7O_2N$: C, 73·1; H, 3·6; N, 7·1%).

Oxidation of 10-acetyl-3-acetoxyphenoxazine. 10-Acetyl-3-acetoxyphenoxazine (100 mg), in ethanol (95%; 5 ml) and 10 N HCl (1 ml) was treated for 3 days at 5° with aqueous sodium nitrite solution (30%; 3 ml). Phenoxazin-3-one (70 mg) was isolated, m.p. and mixed m.p. 206–208° (decomp). λ_{max} 245, 348, 447 mμ (ε, 17·6 × 10^3, 12·8 × 10^3, 11·1 × 10^3). (Found: C, 72·6; H, 3·4; N, 7·3%. Calc. for $C_{12}H_7O_2N$: C, 73·1; H, 3·6; N, 7·1%).

Oxidation of 2-acetylamino-3-acetoxyphenoxazine. 2-Acetylamino-3-acetoxyphenoxazine (150 mg), in ethanol (95%; 20 ml) and 10N HCl (3 ml) was treated at 5° for 2 hr with aqueous sodium

[15] A. Butenandt, J. Keck and G. Neubert, *Liebigs Ann.* **602**, 61 (1957).

nitrate (30%; 10 ml). A yellow solid (135 mg) deposited, which after purification by alumina chromatography and recrystallization from benzene, gave 2-acetylaminophenoxazin-3-one as yellow needles m.p. 274° (decomp) undepressed by an authentic sample prepared after Fischer and Hepp.[16] λ_{max} 240, 400 mμ (ε, 32·6 × 10³, 25·9 × 10³). (Found: C, 65·9; H, 3·9; N, 10·95%. Calc. for $C_{14}H_{10}O_3N_2$ C, 66·1; H, 4·0; N, 11·0%).

Oxidation of 2-*diacetylamino*-3-*acetoxyphenoxazine*. 2-Diacetylamino-3-acetoxyphenoxazine (100 mg), in ethanol (95%; 10 ml) and 10N HCl (1 ml) was treated at 5° for 2 hr with aqueous sodium nitrite (30%; 3 ml). Chloroform extraction of this solution gave an orange product which was purified as above to give 2-acetylaminophenoxazin-3-one, m.p. and mixed m.p. 290° (decomp). λ_{max} 240, 400 mμ (ε, 31·4 × 10³, 24·8 × 10³). (Found: C, 66·3; H, 4·1; N, 11·3%. Calc. for $C_{14}H_{10}O_3N_2$: C, 66·1; H, 4·0; N, 11·0%).

Oxidation of 10-*acetyl*-2-*diacetylamino*-3-*acetoxyphenoxazine*. 10-Acetyl-2-diacetylamino-3-acetoxyphenoxazine (150 mg), in ethanol (95%; 15 ml) and 10N HCl (3 ml) was treated at 5° for 1 hr with aqueous sodium nitrite solution (30%; 8 ml). The precipitated orange solid (120 mg) was purified by recrystallization from benzene. The less soluble fraction yielded 2-acetylaminophenoxazin-3-one (50 mg) m.p. and mixed m.p. 274° (decomp). λ_{max} 240, 400 mμ (ε, 32·6 × 10³, 26·2 × 10³). (Found: C, 66·2; H, 3·9, N, 10·7%. Calc. for $C_{14}H_{10}O_3N_2$: C, 66·1; H, 4·0; N, 11·0%).

The more soluble fraction gave 10-acetyl-2-diacetylamino-3-acetoxyphenoxazine (38 mg), m.p. and mixed m.p. 178–179°. (Found: C, 62·9; H, 4·7; N, 7·5%. Calc. for $C_{20}H_{18}O_6N_2$: C, 62·75; H, 4·75; N, 7·3%).

Oxidation of 2,3-*diacetoxyphenoxazine*. 2,3-Diacetoxyphenoxazine (200 mg), in dioxan (10 ml) and 10N HCl (1 ml) was treated overnight at 5° with aqueous sodium nitrite solution (30%; 4 ml). 2-Acetoxyphenoxazin-3-one (70 mg) was obtained by the usual procedure as red leaflets, m.p. 229–230° (decomp), from benzene–light petroleum. Its m.p. was not depressed by an authentic sample prepared after Diepolder.[13] λ_{max} 245, 363, 448 mμ (ε, 15·2 × 10³, 13·0 × 10³, 9·1 × 10³). (Found: C, 66·0; H, 3·7; N, 5·5%. Calc. for $C_{14}H_9O_4N$: C, 66·0; H. 3·6; N, 5·5%).

Oxidation of 10-*acetyl*-2,3-*diacetoxyphenoxazine*. 10-Acetyl-2,3-diacetoxyphenoxazine (100 mg) in dioxan (8 ml) and 10N HCl (1 ml) was treated at 5° for 36 hr with aqueous sodium nitrite (30% 2 ml). The precipitated red solid gave 2-acetoxyphenoxazin-3-one (50 mg), after recrystallization from benzene–light petroleum, m.p. and mixed m.p. 229–230° (decomp). λ_{max} 245, 359, 447 mμ (ε, 15·2 × 10³, 12·8 × 10³, 9·0 × 10³). (Found: C, 65·9; H, 3·55; N, 5·8%. Calc. for $C_{14}H_9O_4N$: C, 66·0; H, 3·6; N, 5·5%).

Oxidation of 2-*methoxy*-3-*acetoxyphenoxazine*. 2-Methoxy-3-acetoxyphenoxazine (90 mg), in ethanol (95%; 5 ml) and 10N HCl (1 ml) was treated with aqueous sodium nitrite solution (30%; 3 ml). After no apparent reaction occurred at 5° during 3 hr, the reaction mixture was heated at 60° for 5 min. Brown fumes were liberated and the deep orange reaction mixture was allowed to stand at 5° for 2 days. 2-Methoxyphenoxazin-3-one (50 mg) was obtained and purified by sublimation (160–180°/1·0 mm), m.p. and mixed m.p. 255–257°. λ_{max} 222, 390 mμ (ε, 23·1 × 10³, 17·9 × 10³). (Found: C, 68·4, H, 4·0; N, 6·1%. Calc. for $C_{15}H_{11}O_5N$: C, 68·7; H, 4·0; N, 6·2%).

Oxidation of 10-*acetyl*-2-*methoxy*-3-*acetoxyphenoxazine*. 10-Acetyl-2-methoxy-3-acetoxyphenoxazine (70 mg), in ethanol (95%; 5 ml) and 10N HCl (1 ml) was treated with aqueous sodium nitrite solution (30%; 2 ml) at 60° for 5 min and then at 5° for 4 days. 2-Methoxyphenoxazin-3-one (40 mg) was isolated, which after vacuum sublimation (160–180°/1 mm) had m.p. and mixed m.p. 255–257° (decomp). λ_{max} 221, 395 mμ (ε, 24·4 × 10³, 17·2 × 10³). (Found: C, 68·5; H, 3·9; N, 6·15%. Calc. for $C_{15}H_{11}O_5N$: C, 68·7; H, 4·0; N, 6·2%).

[16] O. Fischer and E. Hepp, *Ber. Dtsch. Chem. Ges.* **28**, 293 (1895).

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THEORIE DU POUVOIR ROTATOIRE NATUREL

DANS LA METHODE DES ORBITALES MOLECULAIRES

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Résumé—La méthode des orbitales moléculaires est appliquée à la théorie du pouvoir rotatoire naturel. On démontre que la rotation du plan de polarisation de la lumière est la conséquence du fait que les fonctions moléculaires décrivant les liaisons ne possèdent pas d'axe de révolution ni de plan de symétrie et que la rotation moléculaire est la somme des contributions des liaisons actives et non des centres d'asymétrie. La rotation moléculaire est explicitement calculée en fonction des orbitales atomiques. Son expression montre que la rotation est identiquement nulle si l'on utilise pour orbitales atomiques les orbitales des atomes isolés et que l'on doit admettre que les orbitales du centre d'asymétrie sont perturbées par leur substituant. Les déformations angulaires ne jouent qu'un rôle secondaire. L'application qualitative est faite à la molécule CFClBrI en vue de lier le signe du pouvoir rotatoire à la configuration absolue. Le résultat est en accord avec les règles empiriques actuellement connues. La théorie rend compte de la variation du pouvoir rotatoire avec la température dans les composés acycliques. Est enfin examiné le cas de molécules possédant plusieurs centres d'asymétrie ainsi que celui de molécules actives sans centre d'asymétrie.

Abstract—The M.O. method is applied to the optical rotatory power theory. The rotation of the polarization plane of light is explained by the following reasons: the molecular wave functions describing the bonds have no rotation axis and no plane of symmetry; the molecular rotation comes from the active bonds and not from the asymmetry centers. The expression for the molecular rotation is explicitly given as a function of the atomic orbitals. This expression shows that the rotation is zero if the atomic orbitals one uses are these of the isolated atoms; it also shows that one must take into account the perturbation of the asymmetry center orbitals by the substitutingradicals. The angular deformations play a secondary role. This theory is applied to the CFClBrI molecule with a view to linking the sign of the molecular rotatory power to the configuration. The result is in good agreement with the known empirical rules. For aliphatic compounds this theory explains the variation of the rotatory power with temperature. In the last part we consider molecules with several asymmetry centers and also active molecules without asymmetry centers.

LA traversée d'une substance par une radiation électromagnétique de fréquence ν polarisée rectilignement se traduit par la rotation, éventuellement nulle, du plan de polarisation. La mécanique ondulatoire[1] permet de calculer la rotation moléculaire:

$$\rho = \frac{16\pi^2}{3ch} N \frac{n^2 + 2}{3} \sum_a p_a \sum_b \frac{\nu^2}{\nu_{ab}^2 - \nu^2} R_{ba}$$

c = vitesse de la lumière, h = constante de Planck, N = nombre d'Avogadro, n = constante diélectrique, R_{ba} = force rotatoire de la transition électronique a → b de fréquence ν_{ab}, p_a = probabilité de trouver la molécule dans l'état a. Avec la convention de signe adoptée, ρ est positif pour un composé dextrogyre.

Pratiquement, à la température ordinaire la population des niveaux excités est négligeable si bieu que nous pouvous simplifier l'expression de ρ en ne considérant

[1] Voir par exemple: H. Eyring, J. Walter et G. Kimball, *Quantum Chemistry*. John Wiley, New York (1949); W. Kauzmann, *Quantum Chemistry*. Academic Press, New York (1957).

que les transitions monoélectroniques a → b qui font passer la molécule de son état fondamental a à divers états excités b. Dans ces conditions

$$p_a = 1 \text{ et } \rho = A \sum \frac{\nu^2}{\nu_{ab}^2 - \nu^2} R_{ba}$$

(A = constante positive caractéristique de la substance). Le problème se ramène donc à l'évaluation des forces rotatoires R_{ab} des diverses transitions électroniques possibles.

Nous examinerons d'abord le cas de molécules ne possédant qu'un seul centre d'asymétrie, c'est-à-dire un atome substitué par des groupements tous différents. Après quoi, nous passerons au cas plus complexe de molécules possédant plusieurs centres d'asymétrie.

I. *Molécules ne possédant qu'un seul centre d'asymétrie*

Considérons d'abord pour fixer les idées une molécule saturée constituée d'un atome A lié à quatre atomes B_1, B_2, B_3 et B_4. Pour décrire les fonctions d'onde des liaisons AB_i nous utiliserons des combinaisons linéaires des orbitales atomiques ω des atomes B et χ de l'atome A. Les orbitales χ sont orthogonales entre elles mais les ω et χ ne le sont pas. Pour simplifier les calculs on a avantage à remplacer ces orbitales par des orbitales orthogonalisées selon le procédé de Löwdin.[2] Nous négligerons les intégrales de recouvrement $\int \omega_i \omega_j \, d\tau$ à cause de leur petitesse. On a alors au second ordre:

$$\begin{cases} \omega_i' = \omega_i - \frac{1}{2} \sum_j (\omega_i \chi_j) \chi_j + \cdots = \omega_i - \frac{1}{2} \sum_j s_{ij} \chi_j + \cdots \\ \chi_i' = \chi_i - \frac{1}{2} \sum_j (\chi_i \omega_j) \omega_j + \cdots = \chi_i - \frac{1}{2} \sum_j \sigma_{ij} \omega_j + \cdots \end{cases}$$

en désignant par (ab) l'intégrale de recouvrement $\int ab \, d\tau$. Les orbitales moléculaires orthogonales décrivant chaque liaison AB_i sont:

$$\begin{cases} \varphi_i = \alpha_i \chi_i' + \beta_i \omega_i' & \text{pour l'état fondamental} \\ \varphi_i^* = -\beta_i \chi_i' + \alpha_i \omega_i' & \text{pour l'état excité} \end{cases}$$

Soit:

$$\varphi_i = \alpha_i [\chi_i - \tfrac{1}{2} \sum_j \sigma_{ij} \omega_j] + \beta_i [\omega_i - \tfrac{1}{2} \sum_j s_{ij} \chi_j]$$
$$= (\alpha_i \chi_i + \beta_i \omega_i) - \tfrac{1}{2} \sum_j (\alpha_i \sigma_{ij} \omega_j + \beta_i s_{ij} \chi_j)$$

Si nous utilisons pour construire la fonction moléculaire φ les orbitales χ et ω des atomes isolés, les fonctions χ et ω possèdent en général un axe de révolution, le terme $(\alpha_i \chi_i + \beta_i \omega_i)$ est donc aussi de révolution autour de la droite AB_i, mais il n'en est pas de même pour le second. Tout au plus si les trois atomes B_2, B_3 et B_4 sont identiques, ce terme possède une symétrie d'ordre 3 autour de la droite AB_1. Si deux sont identiques (B_2 et B_3) la fonction possède pour plan de symétrie le plan AB_1B_4. De plus nous savons[3] que pour construire les liaisons σ nous ne pouvons pas utiliser les orbitales des atomes isolés dans leur état fondamental, qu'il faut tenir compte de la perturbation causée par le substituant lui-même qui déforme les orbitales de base en faisant intervenir des orbitales excitées de l'atome si bien que l'ensemble des orbitales χ possèdent la disymétrie imposée par les substituants B. *Les orbitales moléculaires*

[2] P. O. Löwdin, *J. Chem. Phys.* **18**, 365 (1950).
[3] A. Julg, *J. Chim. Phys.* **57**, 19 (1960).

φ et φ^x ne sont donc pas de révolution mais possèdent la symétrie totale de la molécule. Nous admettrons que les centres de gravité des orbitales ω_i' et χ_i' sont alignés avec les noyaux A et B_i.

Le fait que les fonctions moléculaires décrivant les liaisons σ ne sont pas de révolution peut paraître en contradiction avec l'opinion couramment admise. En réalité la contradiction n'est qu'apparente. Lorsqu'on parle de liaison σ on entend orbitale moléculaire localisée construite sur les orbitales atomiques des atomes "chimiquement liés". Mais ces fonctions σ ainsi définies ne sont pas orthogonales et leur produit antisymétrisé ne saurait représenter correctement la molécule. Ici au contraire, nous utilisons des fonctions orthogonales dont l'ensemble décrit correctement la molécule. Mais ce que nous gagnons en rigueur, nous le perdons en compréhension intuitive, les fonctions moléculaires représentant les paires d'électrons dans la molécule ne sont pas localisées entre deux atomes mais font intervenir les atomes voisins. En d'autres termes, les fonctions de liaison ne correspondent pas au trait unissant les atomes dans la symbolique classique.

Les fonctions φ_i ainsi construites étant orthogonales entre elles, l'état fondamental a est décrit par le produit antisymétrisé:

$$\Phi_a = |\varphi_1\bar{\varphi}_1\varphi_2\bar{\varphi}_2\varphi_3\bar{\varphi}_3\varphi_4\bar{\varphi}_4|$$

Un état excité b est obtenu en faisant passer un électron d'une orbitale φ_i sur une orbitale excitée φ_j^x quelconque. Les transitions entre orbitales d'indice différent qui se traduisent par un transfert d'électron d'une liaison sur une autre nécessitent des énergies supérieures à celles d'ionisation des liaisons, c'est-à-dire très supérieures à celles des transitions entre orbitales de même indice. Elles apportent donc une contribution négligeable au pouvoir rotatoire dans le domaine des grandes longeurs d'onde (visible et proche ultra-violet) qui nous occupe ici. Nous nous bornerons donc aux seules transitions entre orbitales de même indice. L'état excité correspondant à $i = j = 4$ par exemple s'écrit:

$$\Phi_b = \frac{1}{\sqrt{2}}\left[|\varphi_1\bar{\varphi}_1\varphi_2\bar{\varphi}_2\varphi_3\bar{\varphi}_3\varphi_4\bar{\varphi}_4^x| + |\varphi_1\bar{\varphi}_1\varphi_2\bar{\varphi}_2\varphi_3\bar{\varphi}_3\varphi_4^x\bar{\varphi}_4|\right]$$

Calcul de la force rotatoire

La force rotatoire R_{ba} s'exprime[1] en fonction des orbitales moléculaires *a* et *b* décrivant les états fondamental et excité par la relation:

$$R_{ba} = \mathrm{Im}[(a|\mathbf{R}|b)\cdot(b|\mathbf{M}|a)$$

$\mathbf{R}$ = représente l'opérateur $e\sum \mathbf{r}_j$

$\mathbf{r}_j$ = rayon vecteur de l'électron j

e = charge de l'électron

et: $$\mathbf{M} = \sum \frac{eh}{i4\pi mc}\,\mathrm{rot.}\,\mathbf{r}_j \qquad (m = \text{masse de l'électron})$$

L'opérateur $\mathbf{R}$ étant la somme d'opérateurs monoélectroniques, $(a|\mathbf{R}|b)$ se réduit à la quantité portant sur les orbitales φ_i et φ_i^x mises en jeu dans la transition. On a donc:

$$(a|\mathbf{R}|b) = (\Phi_a|\sum \mathbf{r}_j|\Phi_b) = \sqrt{2}\int \varphi_i \mathbf{r} \varphi_i^x \, d\tau$$
$$= \sqrt{2}(\alpha_i\chi_i' + \beta_i\omega_i'|\mathbf{r}| - \beta_i\chi_i' + \alpha_i\omega_i')$$

Soit au second ordre en S:

$$(a|\mathbf{R}|b)_l = \sqrt{2}\alpha_l\beta_l[(\omega_l'|\mathbf{r}|\omega_l') - (\chi_l'|\mathbf{r}|\chi_l')] = \sqrt{2}\alpha_l\beta_l\mathbf{G}_{\chi_l'}\mathbf{G}_{\omega_l'}$$

en désignant par $\mathbf{G}_{\chi'}$ et $\mathbf{G}_{\omega'}$ les centres de gravité des orbitales χ' et ω'. Le vecteur $\mathbf{G}_{\chi_l'}\mathbf{G}_{\omega_l'}$ étant porté par la droite AB_l nous écrirons: $(a|\mathbf{R}|b)_l = g_l\mathbf{AB}_l$, g_l étant un coefficient positif déterminé uniquement par les orbitales φ_l et φ_l^{χ} de la liaison AB_l. Pour calculer le vecteur $(b|\mathbf{M}|a)_l$ relatif à la transition $\varphi_l \rightarrow \varphi_l^{\chi}$, il est commode de choisir pour axe des z la droite orientée AB_l. Seule la partie imaginaire m_l de sa composante suivant cet axe intervient dans le calcul de la force rotatoire puisque les autres composantes sont perpendiculaires au vecteur $(a|\mathbf{R}|b)_l = g_l\mathbf{AB}_l$.

$$m_l = \frac{-eh\sqrt{2}}{4\pi mc}\int \varphi_l^{\chi}\left(x\frac{\partial}{\partial y} - y\frac{\partial}{\partial x}\right)\varphi_l\, d\tau = \frac{-eh\sqrt{2}}{4\pi mc}\int \varphi_l^{\chi}\frac{\partial\varphi_l}{\partial\theta}\, d\tau$$

en désignant par θ la variable de repérage angulaire autour de l'axe $\mathbf{AB}_l$. D'où l'expression de la force rotatoire relative à la transition de fréquence ν_l mettant en jeu la liaison AB_l: $R_l = g_l m_l |AB_l|$ et celle du pouvoir rotatoire de la molécule:

$$\rho = A\sum_{l=1\dots4}\frac{\nu^2}{\nu_l^2 - \nu^2}R_l$$

Discussion générale de l'expression de la rotation moléculaire

Remarquons tout d'abord que la force rotatoire étant proportionnelle aux quantités m, si les fonctions φ sont de révolution les dérivées $\dfrac{\partial\varphi}{\partial\theta}$ sont nulles. Les liaisons correspondantes n'apportent aucune contribution au pouvoir rotatoire. On voit donc que l'activité optique est liée à la disymétrie des orbitales moléculaires.

Nous allons maintenant montrer que l'expression ci-dessus de la rotation moléculaire permet de retrouver les propositions classiques.

Examinons d'abord le cas particulier où deux orbitales φ_1 et φ_2 sont identiques, ce qui se produit si les atomes B_1 et B_2 sont de même nature. Les fonctions φ_3 et φ_4 ainsi que φ_3^{χ} et φ_4^{χ} possèdent le plan AB_3B_4 comme plan de symétrie. Si nous développons en série de Fourier ces fonctions φ on a: $\varphi = \Sigma a_n \cos n\theta$ en comptant θ à partir du plan de symétrie. Les dérivées $\dfrac{\partial\varphi}{\partial\theta} = -\sum n\, a_n \sin n\theta$ sont antisymétriques par rapport à ce plan. Les quantités m_3 et m_4 sont donc nulles. D'autre part, les fonctions φ_1 et φ_2 étant par hypothèse identiques, donc de même énergie, forment un système dégénéré. Nous les remplacerons par les combinaisons $\psi_{\pm} = \dfrac{1}{\sqrt{2}}(\varphi_1 \pm \varphi_2)$ pour les états fondamentaux et $\psi_{\pm}^{\chi} = \dfrac{1}{\sqrt{2}}(\varphi_1^{\chi} \pm \varphi_2^{\chi})$ pour les états excités. Les fonctions ψ et ψ^{χ} sont, soit symétriques (signe $+$), soit antisymétrique (signe $-$) par rapport au plan AB_3B_4. Il en résulte que la transition $\psi_+ \rightarrow \psi_+^{\chi}$ entre fonctions possédant un plan de symétrie n'apporte aucune contribution au pouvoir rotatoire ($m = 0$). De même $\psi_- \rightarrow \psi_-^{\chi}$. Pour les transitions entre fonctions de symétrie différente $\psi_+ \rightarrow \psi_-^{\chi}$ et $\psi_- \rightarrow \psi_+^{\chi}$, les répartitions $\psi_+\psi_-^{\chi}$ et $\psi_-\psi_+^{\chi}$ possèdent le plan AB_3B_4 comme plan d'antisymétrie. Les vecteurs $(a|\mathbf{R}|b)$ correspondant sont perpendiculaires à ce plan.

Les valeurs de m le long de l'axe z' de ces vecteurs sont nulles puisque les éléments différentiels $\varphi^x \dfrac{\partial \varphi}{\partial \theta}$ sont deux à deux opposés: $\varphi^x(z') = \varphi^x(-z')$ et $\varphi(z) = -\varphi(-z')$ soit: $\dfrac{\partial \varphi}{\partial \theta}(-z') = -\dfrac{\partial \varphi}{\partial \theta}(z')$.

On verrait de même que les transitions entre orbitales d'indice différents apportent une contribution nulle. D'où la première loi:

"Si la molécule $AB_1B_2B_3B_4$ possède deux liaisons identiques, elle est inactive".

Considérons maintenant deux molécules M_1 et M_2 symétriques par rapport à un plan. Soient φ_{11} et φ_{12} les fonctions correspondant à la même liaison AB_1 dans les deux molécules. Les quantités (a|**R**|b) correspondantes sont égales dans les deux cas à g_1AB_1. Les m sont opposés. En effet on peut écrire en supprimant l'indice i:

$$\begin{cases} \varphi_1 = \Sigma a_{1n} \cos(n\theta - \alpha_{1n}) \\ \varphi_2 = \Sigma a_{2n} \cos(n\theta - \alpha_{2n}) \end{cases} \qquad \begin{cases} \dfrac{\partial \varphi_1}{\partial \theta} = -\Sigma n a_{1n} \sin(n\theta - \alpha_{1n}) \\ \dfrac{\partial \varphi_2}{\partial \theta} = -\Sigma n a_{2n} \sin(n\theta - \alpha_{2n}) \end{cases}$$

Or par hypothèse les fonctions sont symétriques par rapport à un plan donc: $\varphi_2(\theta) = \varphi_1(-\theta)$ c'est-à-dire: $a_{2n} \cos(n\theta - \alpha_{2n}) = a_{1n} \cos(-n\theta - \alpha_{1n}) = a_{1n} \cos(n\theta + \alpha_{1n})$ soit: $a_{2n} = a_{1n}$ et $\alpha_{2n} = -\alpha_{1n}$.

D'où:

$$\frac{\partial \varphi_2(-\theta)}{\partial \theta} = -\Sigma n a_{2n} \sin(-n\theta - \alpha_{2n}) = \Sigma n a_{2n} \sin(n\theta + \alpha_{2n})$$

$$= \Sigma n a_{1n} \sin(n\theta - \alpha_{1n}) = -\frac{\partial \varphi_1}{\partial \theta}(\theta)$$

Comme d'autre part pour les orbitales excitées: $\varphi_2{}^x(\theta) = \varphi_1{}^x(-\theta)$ on en conclut: $\int \varphi_{12}{}^x \dfrac{\partial}{\partial \theta} \varphi_{12}\, d\tau = -\int \varphi_{11}{}^x \dfrac{\partial}{\partial \theta} \varphi_{11}\, d\tau$ c'est-à-dire: $m_{12} = -m_{11}$. D'où la seconde loi:

"Dans deux molécules symétriques par rapport à un plan les contributions de chaque transition, donc les pouvoirs rotatoires sont opposés".

Nous avons supposé que l'ensemble des deux molécules possédaient un plan de symétrie. Si, inverses au sens de la stéréochimie classique, elles ne possèdent pas ce plan, on peut toujours se ramener à ce cas par un déplacement qui naturellement laisse inchangée la valeur de la rotation moléculaire.

Calcul de m_i *en fonction des orbitales atomiques*

Pour plus de généralité nous introduirons les orbitales t_{kj} des atomes B_k n'intervenant pas directement dans la liaison avec A. Au second ordre près, nous avons:

$$\begin{cases} \omega_1' = \omega_1 - \frac{1}{2}(\omega_1\chi_1)\chi_1 - \frac{1}{2}\sum_k (\omega_1\chi_k)\chi_k \\ \chi_1' = \chi_1 - \frac{1}{2}(\omega_1\chi_1)\omega_1 - \frac{1}{2}\sum_k (\chi_1\omega_k)\omega_k - \frac{1}{2}\sum_j (\chi_1 t_{1j})t_{1j} \end{cases}$$

VOL. 12 1961

Soit en posant: $S = (\omega_1\chi_1)$, $s_k = (\omega_1\chi_k)$, $\sigma_k = (\chi_1\omega_k)$ et $r_j = (\chi_1 t_{1j})$

$$\begin{cases}\omega_1' = \omega_1 - \frac{1}{2}S\chi_1 - \frac{1}{2}\sum s_k\chi_k \\ \chi_1' = \chi_1 - \frac{1}{2}S\omega_1 - \frac{1}{2}\sum \sigma_k\omega_k - \frac{1}{2}\sum_j r_j t_{1j}\end{cases}$$

Supposons que les diverses orbitales ω et χ soient de révolution autour de leurs axes principaux. En posant: $A_1 = \sum_j r_j t_{1j}$

$$\varphi = \alpha[\chi_1 - \tfrac{1}{2}S\omega_1 - \tfrac{1}{2}\sum \sigma_k\omega_k - \tfrac{1}{2}A_1] + \beta[\omega_1 - \tfrac{1}{2}S\chi_1 - \tfrac{1}{2}\sum s_k\chi_k]$$

$$= (\text{fonction de révolution}) - \frac{\alpha}{2}A_1 - \frac{\alpha}{2}\sum \sigma_k\omega_k - \frac{\beta}{2}\sum s_k\chi_k$$

soit:
$$\frac{\partial\varphi}{\partial\theta} = -\frac{\alpha}{2}\frac{\partial A_1}{\partial\theta} - \frac{\alpha}{2}\sum \sigma_k\frac{\partial\omega_k}{\partial\theta} - \frac{\beta}{2}\sum s_k\frac{\partial\chi_k}{\partial\theta}$$

Si les orbitales t_{1j} sont identiques ou forment un système de révolution, ce qui arrive si l'atome B_1 est monovalent (hydrogène, halogènes) ou substitué par des radicaux monovalents symétriques (par exemple si B_1 est un carbone sp_3 d'un groupement méthyle), la dérivée $\frac{\partial A_1}{\partial\theta}$ est nulle. Dans le cas contraire, puisque B_1 n'est pas un centre d'asymétrie, A possède un plan de symétrie (c'est le cas d'un atome d'oxygène alcoolique). La dérivée $\frac{\partial A_1}{\partial\theta}$ possède alors un plan d'antisymétrie. Mais si la rotation autour de la liaison AB, est parfaitement libre la valeur moyenne de A_1 est de révolution et l'on est ramené au premier cas.

D'autre part: $\varphi^\chi = -\beta\chi_1' + \alpha\omega_1'$

$$= -\beta[\chi_1 - \tfrac{1}{2}S\omega_1 - \tfrac{1}{2}\sum \sigma_k\omega_k - \tfrac{1}{2}A_1] + \alpha[\omega_1 - \tfrac{1}{2}S\chi_1 - \tfrac{1}{2}\sum s_k\chi_k]$$

$$= (\text{fonction de révolution}) + \frac{\beta}{2}A_1 + \tfrac{1}{2}\sum_k(\beta\sigma_k\omega_k - \alpha s_k\chi_k)$$

Dans le calcul de $\int \varphi^\chi \frac{\partial\varphi}{\partial\theta}\,d\tau$ s'introduisent des termes tels que $\int$(fct. de révol.) $\frac{\partial\omega_k}{\partial\theta}\,d\tau$ ou $\int$(fct. de révol.) $\frac{\partial\chi_k}{\partial\theta}\,d\tau$ qui sont nuls ainsi que $\int$(fct. de révol.) $\frac{\partial A_1}{\partial\theta}\,d\tau$, si A_1 possède un plan de symétrie. De même $\int A_1\frac{\partial A_1}{\partial\theta}\,d\tau$ dans tous les cas. Reste:

$$-\tfrac{1}{2}\left[\alpha\frac{\partial A_1}{\partial\theta} + \alpha\sum\sigma_k\frac{\partial\omega_k}{\partial\theta} + \beta\sum s_k\frac{\partial\chi_k}{\partial\theta}\right]\cdot\tfrac{1}{2}\left[\beta A_1 + \sum_1(\beta\sigma_1\omega_1 - \alpha s_1\chi_1)\right]$$

$$= \left\{-\tfrac{1}{4}\left[\alpha\beta\sum_k\sum_1\left(\sigma_k\sigma_1\frac{\partial\omega_k}{\partial\theta}\omega_1 - s_k s_1\frac{\partial\chi_k}{\partial\theta}\chi_1\right) - \alpha^2\sum_k\sum_1\sigma_k s_1\frac{\partial\omega_k}{\partial\theta}\chi_1\right.\right.$$

$$\left. + \beta^2\sum_k\sum_1\sigma_1 s_k\frac{\partial\chi_k}{\partial\theta}\omega_1\right] - \tfrac{1}{4}\left[\alpha\frac{\partial A_1}{\partial\theta}\sum_1(\beta\sigma_1\omega_1 - \alpha s_1\chi_1)\right.$$

$$\left.\left. + \alpha\beta\sum_k\sigma_k A_1\frac{\partial\omega_k}{\partial\theta} + \beta^2\sum_k s_k A_1\frac{\partial\chi_k}{\partial\theta}\right]\right\}$$

Mais: $\sum_k \sum_l \sigma_k \sigma_l \frac{\partial \omega_k}{\partial \theta} \omega_l$ donne: $\sum_{(kl)} \sigma_k \sigma_l \left(\frac{\partial \omega_k}{\partial \theta} \omega_l + \frac{\partial \omega_l}{\partial \theta} \omega_k \right) = \sum_{(kl)} \sigma_k \sigma_l \frac{\partial}{\partial \theta} (\omega_k \omega_l)$

car: $$\int \frac{\partial \omega_k}{\partial \theta} \omega_k \, d\tau = 0$$

et $$\int \frac{\partial}{\partial \theta} (\omega_k \omega_l) \, d\tau = \int_0^{2\pi} \frac{\partial}{\partial \theta} [\iint \omega_k \omega_l r^2 \, dr \sin \psi \, d\psi] \, d\theta$$

(en coordonnées sphériques r, θ, ψ)

$$= [\iint \omega_k \omega_l r^2 \, dr \sin \psi \, d\psi]_0^{2\pi} = 0$$

De même pour le terme $\sum_k \sum_l s_k s_l \frac{\partial \chi_k}{\partial \theta} \chi_l$. Le premier crochet se réduit donc à:

$$\tfrac{1}{4} \left[\alpha^2 \sum_k \sum_l \sigma_k s_l \frac{\partial \omega_k}{\partial \theta} \chi_l - \beta^2 \sum_k \sum_l \sigma_l s_k \frac{\partial \chi_k}{\partial \theta} \omega_l \right] = \tfrac{1}{4} \sum_k \sum_l \sigma_k s_l \left(\alpha^2 \frac{\partial \omega_k}{\partial \theta} \chi_l - \beta^2 \omega_k \frac{\partial \chi_l}{\partial \theta} \right)$$

Mais: $$\int \frac{\partial}{\partial \theta} (\omega_k \chi_l) \, d\tau = \int \frac{\partial \omega_k}{\partial \theta} \chi_l \, d\tau + \int \frac{\partial \chi_l}{\partial \theta} \omega_k \, d\tau = 0$$

Reste donc: $\tfrac{1}{4} \sum_k \sum_l \sigma_k s_l \int \frac{\partial \omega_k}{\partial \theta} \chi_l \, d\tau = -\tfrac{1}{4} \sum_k \sum_l \sigma_k s_l \int \omega_k \frac{\partial \chi_l}{\partial \theta} \, d\tau$ car: $\alpha^2 + \beta^2 = 1$.

De même le second crochet se réduit à: $-\tfrac{1}{4} \sum s_k \int A_l \frac{\partial \chi_k}{\partial \theta} \, d\tau$. Si A_l (ou sa valeur moyenne) est de révolution, ce terme est nul. Nous nous bornerons pour l'instant à ce cas.

L'introduction dans le développement des orbitales atomiques de termes du second ordre par rapport aux intégrales de recouvrement revient à multiplier les coefficients des orbitales réelles par des facteurs de la forme $(1 + \varepsilon)$, ε étant du premier ordre par rapport aux intégrales de recouvrement. L'expression ci-dessus est donc valable au troisième ordre par rapport à celles-ci.

Numérotons les atomes B_k dans le sens positif des θ croissants: $k - 1$, k, $k + 1$.

On a: $$\int \varphi^x \frac{\partial \varphi}{\partial \theta} \, d\tau = -\tfrac{1}{4} \sum_k \sigma_k \int \omega_k \left[s_{k-1} \frac{\partial \chi_{k-1}}{\partial \theta} + s_k \frac{\partial \chi_k}{\partial \theta} + s_{k+1} \frac{\partial \chi_{k+1}}{\partial \theta} \right] d\tau$$

$$= -\tfrac{1}{4} \sum_k \sigma_k \int \omega_k \frac{\partial}{\partial \theta} [s_{k-1} \chi_{k-1} + s_{k+1} \chi_{k+1}] \, d\tau$$

Si les orbitales χ sont identiques, c'est-à-dire si l'on construit les orbitales moléculaires sur des fonctions atomiques non perturbées, $\int \omega_k \frac{\partial \chi_{k-1}}{\partial \theta} \, d\tau = -\int \omega_k \frac{\partial \chi_{k+1}}{\partial \theta} \, d\tau$ et $s_{k-1} = s_{k+1}$, l'intégrale $\int \varphi^x \frac{\partial \varphi}{\partial \theta} \, d\tau$ est nulle. On voit donc que l'existence du pouvoir rotatoire est liée à la *déformation des orbitales atomiques sous l'effet du substituant*. Pour introduire la déformation de ces orbitales nous supposerons que les orbitales χ sont de la forme: $\chi_k = \chi_k^0 + \lambda_k \xi_k^0$.

χ_k^0 est l'orbitale non perturbée. ξ_k^0 est une orbitale excitée orthogonale de même symétrie sp_3 que χ_k^0 c'est-à-dire en particulier pointant dans la même direction que χ_k^0, construite sur des orbitales atomiques supérieures. Les orbitales χ_k^0 sont donc

égales entre elles, de même les ξ_k^0. λ_k est un nombre petit devant l'unité. De même nous poserons: $s_k = s_k^0 + \lambda_k s_k' = s + \lambda_k s'$ en désignant par s' l'intégrale de recouvrement $(\omega_1 \xi_k^0)$.

$$\int q^x \frac{\partial q}{\partial \theta}\, d\tau = -\tfrac{1}{4} \sum_k \sigma_k \Big[(s + \lambda_{k-1} s') \int \omega_k \frac{\partial}{\partial \theta} (\chi_{k-1}^0 + \lambda_{k-1} \xi_{k-1}^0)\, d\tau + \cdots$$

$$\cdots + (s + \lambda_{k+1} s') \int \omega_k \frac{\partial}{\partial \theta} (\chi_{k+1}^0 + \lambda_{k+1} \xi_{k+1}^0)\, d\tau$$

$$= -\tfrac{1}{4} \sum \sigma_k (\lambda_{k-1} - \lambda_{k+1}) \int \omega_k \left(s' \frac{\partial \chi_{k-1}^0}{\partial \theta} + s \frac{\partial \xi_{k-1}^0}{\partial \theta} \right) d\tau$$

Les intégrales $\int \omega_k \frac{\partial \chi_{k-1}^0}{\partial \theta}\, d\tau$ et $\int \omega_k \frac{\partial \xi_{k-1}^0}{\partial \theta}\, d\tau$ sont négatives ainsi que les s et σ. Nous écrirons pour abréger: $\int q^x \frac{\partial q}{\partial \theta}\, d\tau = -\frac{1}{4} \sum_k \sigma_k (\lambda_{k-1} - \lambda_{k+1}) I_k$ (avec $I_k > 0$).

On vérifiera sans peine sur cette expression que si deux atomes B_k sont de même nature que $\rho = \Sigma \rho_i = 0$.

Influence des déformations angulaires

Dans ce qui précède nous avons supposé que les quatre orbitales χ_k formaient un faisceau régulier. En réalité lorsque les substituants B sont différents le faisceau n'est pas régulier mais les déformations angulaires qui en résultent sont très faibles, quelques degrés au maximum. Raisonnons sur des orbitales χ_k, hybrides sp_3 disymétriques, sans faire appel à des niveaux atomiques supérieurs. Les orbitales χ_k sont de la forme: $\chi_k^0 + \sum_{i \neq k} c_i \chi_k^0$, les coefficients c étant des infiniment petit du premier ordre. Ces orbitales sont encore de révolution. Choisissons comme axe des z l'axe de χ_1 et plaçons l'atome B_3 par exemple dans le plan $x = 0$, on a:

$$\begin{cases} \chi_1 = \chi_1^0 + a(\chi_2^0 + \chi_3^0 + \chi_4^0) \\ \chi_2 = \chi_2^0 - a\chi_1^0 + b\chi_3^0 - c\chi_4^0 \\ \chi_3 = \chi_3^0 - a\chi_1^0 - b(\chi_2^0 + \chi_4^0) \\ \chi_4 = \chi_4^0 - a\chi_1^0 + c\chi_2^0 + b\chi_3^0 \end{cases}$$

a, b, c étant des coefficients déterminés par la géométrie de la molécule.

$$\begin{cases} s_2 = (\omega_1 \chi_2) = (\omega_1 \chi_2^0) - a(\omega_1 \chi_1^0) + b(\omega_1 \chi_3^0) - c(\omega_1 \chi_4^0) = s(1 - a + b - c) \\ s_4 = (\omega_1 \chi_4) = (\omega_1 \chi_4^0) - a(\omega_1 \chi_1^0) + b(\omega_1 \chi_3^0) + c(\omega_1 \chi_4^0) = s(1 - a + b + c) \end{cases}$$

$$\int \omega_3 \frac{\partial \chi_2}{\partial \theta}\, d\tau = \int \omega_3 \frac{\partial}{\partial \theta} (\chi_2^0 - c\chi_4^0)\, d\tau = (1 + c) \int \omega_3 \frac{\partial \chi_2^0}{\partial \theta}\, d\tau$$

$$\int \omega_3 \frac{\partial \chi_4}{\partial \theta}\, d\tau = \int \omega_3 \frac{\partial}{\partial \theta} (\chi_4^0 + c\chi_2^0)\, d\tau = (-1 + c) \int \omega_3 \frac{\partial \chi_2^0}{\partial \theta}\, d\tau$$

Soit:

$$\int \omega_3 \frac{\partial}{\partial \theta} (s_2 \chi_2 + s_4 \chi_4)\, d\tau = s[(1 - a + b - c)(1 + c) + (1 - a + b + c)(-1 + c)] \int \omega_3 \frac{\partial \chi_2^0}{\partial \theta}\, d\tau = 0$$

au second ordre. Il en est de même pour les intégrales correspondant à B_2 et B_4. La déformation angulaire n'intervient qu'au second ordre, elle est donc négligeable devant l'effet de déformation des orbitales par les substituants.

Evaluation des différences $\lambda_{k-1} - \lambda_{k+1}$

La détermination des λ pose le problème général du traitement des liaisons σ. Considérons la liaison A — B. Placée dans le voisinage de l'atome neutre B, l'orbitale χ de l'atome A pointant vers B se déforme. Désignons par a et b les orbitales perturbées des atomes A et B. La théorie du champ self-consistent introduit entre autres les quantités:[4]

$$\begin{cases} I_{ab} = SW_a + (B^+, ab) \\ I_{ba} = SW_b + (A^+, ab) \end{cases}$$

Soit en introduisant les potentiels A et B créés par les atomes neutres et les intégrales ioniques que nous développerons au second ordre par rapport à l'intégrale de recouvrement S selon la formule de Mulliken:[5]

$$I_{ab} = SW_a + (B, ab) - (bb, ab) = S[W_a - \tfrac{1}{2}(b^2, b^2] - \tfrac{1}{2}S(a^2, b^2) + (B, ab)$$

De même: $\quad I_{ba} = S[W_b - \tfrac{1}{2}(a^2, a^2)] - \tfrac{1}{2}S(a^2, b^2) + (A, ab)$

Ces quantités devraient être égales à cause de l'hermiticité des opérateurs. En réalité lorsqu'on utilise des orbitales de Slater non perturbées, cette égalité n'est pas satisfaite. Ce phénomène se rencontre même pour les orbitales π, par exemple à propos du groupement carbonyle lorsqu'on ne prend pas pour les orbitales π des Z correspondant aux charges nettes des atomes.[6] Nous admettrons que la vérification de cette égalité nécessaire est un critère de validité pour les orbitales atomiques.

En négligeant la différence entre les intégrales (B, ab) et (A, ab), $I_{ab} = I_{ba}$ entraine: $W_a + \frac{1}{2}(a^2, a^2) = W_b + \frac{1}{2}(b^2, b^2)$, c'est-à-dire que les électronégativités ε des orbitales a et b au sens de Mulliken[7] sont égales. En effet en négligeant la variation d'ionicité dans l'atome neutre et les ions:[8] $W = -\mathscr{T}$ ($\mathscr{T}$ = énergie d'ionisation) et l'intégrale coulombienne monocentrique $J = \mathscr{T} - \mathscr{A}$ ($\mathscr{A}$ = affinité électronique), c'est-à-dire: $W + \frac{1}{2}J = -\frac{1}{2}(\mathscr{T} + \mathscr{A}) = -\varepsilon$. Les éléments de matrice L_{aa} et L_{bb} sont égaux, il n'y a pas de déplacement de charge le long de la liaison. Le moment de la liaison AB se réduit donc aux seuls moments atomiques, non nuls puisque les centres de gravité des orbitales a et b ne coincident pas avec les noyaux A et B.

En réalité le calcul précédent n'est qu'approximatif, les électronégativités des orbitales a et b ne sont certainement pas rigoureusement égales et il y a un léger déplacement de charge. Cependant il montre la "tendance" qu'ont les électronégativités des orbitales a et b à se rapprocher.

L'énergie d'un électron sur l'orbitale perturbée $\chi + \lambda\xi$ est:

$$W_{\chi+\lambda\xi} = (H \mid \chi^2 + 2\lambda\chi\xi + \lambda^2\xi^2) = W_\chi + \lambda^2 W_\xi$$

De même l'intégrale coulombienne correspondante est:

$$J_{(\chi+\lambda\xi)} = (\chi^2 + 2\lambda\chi\xi + \lambda^2\xi^2 \mid \chi^2 + 2\lambda\chi\xi + \lambda^2\xi^2) = J_{\chi^2} + 4\lambda(\chi^2, {}_\chi\xi) + \lambda^2(\cdots)$$

[4] pour les notations voir par exemple: G. Berthier, *J. Chim. Phys.* **50**, 344 (1953).
[5] R. S. Mulliken, *J. Chim. Phys.* **46**, 500 et 521 (1949).
[6] A. Julg et M. Bonnet, *J. Chim. Phys.* **57**, 434 (1960).
[7] R. S. Mulliken, *J. Chem. Phys.* **54**, 3570 (1932).
[8] A. Julg, *J. Chim. Phys.* **55**, 413 (1958).

Soit au second ordre: $\varepsilon_{\chi+\lambda\xi} = \varepsilon_\chi - 2\lambda(\chi^2, {}_\chi\xi)$

Supposons pour fixer les idées (ce sera en général le cas qui nous interessera) que l'électronégativité de l'atome B non perturbée soit supérieure à celle de l'atome A non perturbé. Dans la molécule, l'électronégativité de l'orbitale a doit être supérieure à celle de l'orbitale dans l'atome A non perturbé. C'est-à-dire: $\lambda_A < 0$ et $\lambda_B > 0$. D'autre part la perturbation est d'autant plus grande que la difference des électronégativités des atomes A et B est plus grande. Si bien qu'ici pour les diverses liaisons AB_k aboutissant à des orbitales initialement identiques de l'atome A nous prendrons $(\lambda_{k-1} - \lambda_{k+1})$ proportionnel à $(\varepsilon_{k+1} - \varepsilon_{k-1})$, les λ étant négatifs.

Relation entre le signe du pouvoir rotatoire et la configuration absolue

C'est certainement le problème le plus important que d'essayer de relier le signe du pouvoir rotatoire à la géométrie de la molécule. Plusieurs tentatives ont été faites.[9,10] En principe, les expressions proposées ici doivent permettre de résoudre le problème. Mais il est difficile pour l'instant de donner des règles générales, les quantités intervenant dans l'expression de ρ ne se prêtant pas à des interprétations évidentes. Une approche est cependant possible. L'expression de la rotation moléculaire $\rho = A \sum \frac{\nu^2}{\nu_i^2 - \nu^2} R_i$ montre que pour une fréquence légèrement inférieure à la plus basse fréquence d'absorption, ρ a le signe de la force rotatoire R_i correspondant à cette transition. Le signe du pouvoir rotatoire dans cette région est donc celui de la somme: $\sum_k \sigma_k I_k(\lambda_{k-1} - \lambda_{k+1})$ correspondant à la première transition. Or l'énergie de transition dans un système A — B varie dans le même sens que la différence des électronégativités respectives des atomes A et B. Avec nos notations nous devons choisir pour atome B_1 l'atome dont l'électronégativité est la plus voisine de celle de l'atome central A.

Pour aller plus loin, nous prendrons un exemple, celui de la molécule CFClBrI représentée sur la figure. La première transition correspond à la liaison C — I. Les

électronégativités des atomes Cl et Br étant peu différentes par rapport à celle du fluor, on peut, en première approximation admettre $\lambda_{Cl} = \lambda_{Br}$. Le signe de ρ est donc celui de:

$$-|\sigma_{\varphi}| I_{\varphi}(\lambda_F - \lambda_{Br}) + |\sigma_{Br}| I_{Br}(\lambda_{Cl} - \lambda_F)$$

c'est-à-dire celui de:

$$(\lambda_F - \lambda_{Br})[|\sigma_{Br}| I_{Br} - |\sigma_{Cl}| I_{Cl}].$$

L'évaluation des quantités I n'est pas simple. Toutefois il est certain qu'elles varient dans le même sens que les intégrales de recouvrement σ. Donc le signe de ρ est

[9] voir par exemple: J. P. Mathieu, *Les Théories Moléculaires du Pouvoir Rotatoire Naturel*. Gauthier-Villars, Paris (1946). *Handbuch der Physik* **28**, 333 (1957).
[10] J. H. Brewster, *J. Amer. Chem. Soc.* **81**, 5475 (1959).

celui de $(\lambda_F - \lambda_{Br})(\sigma_{Br}^2 - \sigma_{Cl}^2)$ c'est-à-dire celui de $(\lambda_{Br} - \lambda_F)$ ou encore celui de $(\varepsilon_F - \varepsilon_{Br})$. Le composé envisagé est donc *dextrogyre*.

Expérimentalement il n'est pas possible de savoir si cette prévision est conforme à la réalité. Cependant si l'on applique la règle de Boys[9] qui dit que "l'isomère dextrogyre est celui pour lequel l'observateur, placé au centre du groupe le plus volumineux (I), voit les trois autres groupes pris par ordre de taille décroissante (Br, Cl, F) disposés dans le sens de rotation des aiguilles d'une montre", on est conduit au même résultat. D'après la règle empirique de Brewster[10] qui lie le phénomène à la polarisabilité des substituants (il suffit dans la règle de Boys de remplacer les mots "plus volumineux" et "taille décroissante" par "le plus polarisable" et "polarisabilité décroissante"), le composé envisagé est aussi dextrogyre. Il semble donc qu'il n'y ait pas de doute possible sur le signe de la rotation moléculaire dans le visible.

Les règles de Boys ou de Brewster, sourtout celles de ce dernier, malgré leur simplicité ne sont peut-être pas absoluement générales comme notre formule mais elles ont l'avantage d'être directement utilisables alors que le calcul très approximatif que nous avons fait ici n'est pas applicable dans tous les cas.

Influence de la température

Nous avons vu plus haut que si la rotation n'est pas parfaitement libre pour le groupement B_1, dans le calcul de m_1 s'introduit un terme supplémentaire:

$$-\tfrac{1}{4} \sum s_k \int A_1 \frac{\partial \chi_k}{\partial \theta} \, d\tau.$$

Ici encore on voit que si toutes les orbitales χ_k sont égales cette expression est identiquement nulle: $\dfrac{\partial}{\partial \theta}(\Sigma \chi_k) = 0$. Avec les notations précédentes on a au second ordre:

$$-\tfrac{1}{4} \sum (s + \lambda_k s') \int A_1 \frac{\partial}{\partial \theta} (\chi_k^0 + \lambda_k \xi_k^0) \, d\tau = -\tfrac{1}{4} \sum \lambda_k \int A_1 \left(s \frac{\partial \xi_k^0}{\partial \theta} + s' \frac{\partial \chi_k^0}{\partial \theta} \right) d\tau$$

Si la rotation n'est pas libre, la molécule possède des conformations privilégiées pour lesquelles le plan de symétrie de A passe par un atome B_k, B_5 par exemple. Les intégrales $\int A_1 \dfrac{\partial \xi_3^0}{\partial \theta} \, d\tau$ et $\int A_1 \dfrac{\partial \chi_3^0}{\partial \theta} \, d\tau$ sont nulles par raison de symétrie. Reste:

$$-\tfrac{1}{4} \left[\lambda_2 \int A_1 \frac{\partial}{\partial \theta} (s\xi_2^0 + s'\chi_2^0) \, d\tau + \lambda_4 \int A_1 \frac{\partial}{\partial \theta} (s\xi_4^0 + s'\chi_4^0) \, d\tau \right.$$

$$\left. = -\tfrac{1}{4} (\lambda_2 - \lambda_4) \int A_1 \frac{\partial}{\partial \theta} (s\xi_2^0 + s'\chi_2^0) = -\tfrac{1}{4} (\lambda_2 - \lambda_4) J \right]$$

La résultante du système A étant en *trans* par rapport à l'atome B_3, les intégrales $\int A_1 \dfrac{\partial \xi_2^0}{\partial \theta} \, d\tau$ et $\int A_1 \dfrac{\partial \chi_2^0}{\partial \theta} \, d\tau$ sont positives et J est négatif.

$$\int q^z \frac{\partial q}{\partial \theta} \, d\tau = -\tfrac{1}{4} \left[\sigma_2 I_2 (\lambda_4 - \lambda_3) + \sigma_4 I_4 (\lambda_3 - \lambda_2) + \sigma_3 I_3 (\lambda_2 - \lambda_4) \left(1 + \frac{J}{\sigma_3 I_3} \right) \right]$$

On obtient des expressions analogues si le plan de symétrie de A_1 passe par B_2 ou B_4. Dans la plupart des cas les énergies des diverses configurations stables sont très voisines si bien que nous pouvons admettre sans grande erreur que toutes les configurations décalées sont également probables, les autres configurations étant pratiquement interdites. En d'autres termes, la rotation moléculaire observée macroscopiquement est la moyenne des rotations correspondant à chacune des conformations stables. Soit:

$$\sigma_2 I_2(\lambda_4 - \lambda_3)\left(1 + \frac{J}{3\sigma_2 I_2}\right) + \sigma_4 I_4(\lambda_3 - \lambda_2)\left(1 + \frac{J}{3\sigma_4 I_4}\right) + \sigma_3 I_3(\lambda_2 - \lambda_4)\left(1 + \frac{J}{3\sigma_3 I_3}\right)$$

En négligeant la différence entre les divers termes correctifs $\frac{J}{3\sigma_k I_k}$, on voit que la rotation moléculaire est multipliée par un facteur plus grand que 1. On en conclut que, quel que soit son signe, le pouvoir rotatoire est supérieur. Une élévation de température, qui fait disparaitre les conformations privilégiées, doit donc se traduire par une diminution du pouvoir rotatoire. C'est ce qu'on observe généralement pour les chaines aliphatiques.[11]

Remarque sur l'influence des liaisons hydrogène

L'effet de la température est encore plus marqué si des liaisons inter- ou intramoléculaires, liaison hydrogène par exemple, viennent à basse température interdire la rotation. A l'effet de blocage de la rotation s'ajoute une perturbation notable des orbitales due à un effet induit (modification des charges atomiques) et à un effet de champ créé par le groupement porteur de l'hydrogène lié (OH par exemple). Ainsi pour l'acide lactique, à 15° pour $\lambda = 5461$ A°, $\rho = -2{\cdot}0°$ mais à 70° $\rho = +0{\cdot}6°$. Ici la modification causée par la liaison hydrogène est en valeur absolue supérieure à la valeur du pouvoir rotatoire ce qui explique l'inversion du signe qui se produit vers 50°.[12] La dilution peut aussi jouer le même rôle en modifiant les liaisons hydrogène. C'est le cas du lactate de méthyle. Pur, $\alpha_D = +7{\cdot}46°$ alors qu'en solution dans l'eau le pouvoir rotatoire décroit avec la dilution, la limite étant atteinte pour des solutions à 10%.[13]

$$\alpha(80\%) = +4{\cdot}1°$$
$$\alpha(51\%) = +2{\cdot}1$$
$$\alpha(20\%) = +1{\cdot}8$$
$$\alpha(10\%) = +1{\cdot}3$$

Il en est de même pour le comportement qualifié d'anormal de l'acide malique naturel[13]

$\rho_D = -3{\cdot}3°$ en solution aqueuse à 8.4%
$0{\cdot}0$ en solution aqueuse à 34%
$+4.7$ en solution aqueuse à 80%

La deutération diminue la force des liaisons hydrogène, on doit donc s'attendre à une modification de la rotation moléculaire. Effectivement la rotation moléculaire de l'acide D-mandélique: C_6H_5—C(OH)H—CO_2H à 20° dans l'acétophénone pour la

[11] W. Kauzmann et H. Eyring, *J. Chem. Phys.* **9**, 41 (1941).
[12] G. W. Clough, *J. Chem. Soc.* **113**, 526 (1918).
[13] L. Fieser et M. Fieser, *Organic Chemistry* (3rd Ed.) Reinhold, New York (1956).

raie 5893 Å vaut $-272{\cdot}2°$ alors que pour la molécule deutérée: $C_6H_5—C(OD)H—CO_2D$ elle vaut $-266{\cdot}7°$. De même pour l'acide L-atropique dans les mêmes conditions la rotation moléculaire passe de $+63{\cdot}1$ à $61{\cdot}8$.[14] La preuve que c'est bien la disparition ou tout au moins l'affaiblissement des liaisons hydrogène qui est responsable de cette variation, c'est que dans la molécule d'alcool octylique secondaire (ROH), la rotation est pratiquement la même que pour l'alcool deutéré (ROD): $15{\cdot}23°$ contre $15{\cdot}34$ à $17°$ pour la raie 5461 Å.[15]

Remarque sur la nature de l'atome A

Nous avons jusqu'ici supposé l'atome A lié à quatre atomes B. C'est le cas d'un carbone hybridé en sp_3 ou de l'azote sp_3 d'un ammonium quaternaire. Les mêmes raisonnements s'appliquent à des porteurs de quatre orbitales φ_1 n'entrant pas nécessairement dans une liaison. Par exemple dans les amines où une orbitale φ se réduit à l'orbitale atomique de l'atome d'azote occupée par le doublet libre. La première transition est due au doublet: passage d'un électron sur un niveau atomique supérieur. La molécule sera active si les trois substituants de l'azote sont différents. On sait que si l'on n'observe pas d'activité optique c'est parce que les mesures faites à l'échelle macroscopique portent sur un nombre égal de molécules inverses provenant du renversement facile du trièdre des substituants. Cependant il est intéressant de noter que l'expression de la contribution apportée par le doublet est différente de celle apportée par une liaison. Les états décrivant le doublet sont:

$$\begin{cases} \varphi_1 = \chi_1 - \frac{1}{2}\sum \sigma_k \omega_k \\ \varphi_1{}^x = \chi_1{}^x - \frac{1}{2}\sum \sigma_k{}^x \omega_k \end{cases}$$

avec $\sigma_k{}^x = (\chi_1{}^x \omega_k)$. D'où:

$$\left(\varphi_1{}^x \frac{\partial \varphi_1}{\partial \theta}\right) = \frac{1}{4}\sum_k \sum_l \sigma_k{}^x \sigma_l \left(\omega_k \frac{\partial \omega_l}{\partial \theta}\right) = \frac{1}{4}\sum_k \sigma_k{}^x \left(\omega_k \frac{\partial}{\partial \theta}\left[\sigma_{k-1}\omega_{k-1} + \sigma_{k+1}\omega_{k+1}\right]\right)$$

Dans un oxygène, type alcool ou éther-oxyde, deux doublets occupent deux orbitales que l'on peut decrire par des fonctions identiques (hybridation sp_3). L'atome d'oxygène n'est donc pas centre d'asymétrie. De même un atome de carbone hybridé en sp_2, les quatre fonctions σ et π possédant normalement un plan de symétrie, celui des trois liaisons σ.

Enfin la théorie se généralise aux atomes substitués plus de quatre fois comme dans les complexes métalliques. Mais à côté des six liaisons σ des complexes hexacoordinés il faut faire intervenir les trois doublets occupant les trois orbitales *d* non hybridées. Celles-ci sont aussi déformées de façon à refléter la disymétrie de la molécule. Si tous les substituants (l'un d'eux pouvant d'ailleurs se réduire à une orbitale occupée par un doublet non lié) sont différents, le complexe est actif. Si deux substituants diamétralement opposés par rapport à l'atome central sont identiques, par raison de symétrie ces deux substituants utilisent les deux orbitales identiques hybrides 4s, $4p_z$, $3d_{z^2}$ (dans le cas où l'atome central est un métal de transition de la quatrième ligne). Les fonctions de liaisons des quatre autres substituants possèdent le plan $z = 0$ de ces derniers comme plan de symétrie ainsi que le doublet libre $3d_{xy}$. Les orbitales d_{yz} et $-d_{xz}$ décrivant les autres doublets sont

[14] H. Erlenmeyer et H. Schenkel, *Helv. Chim. Acta* **19**, 1199 (1936).
[15] L. Young et C. W. Porter, *J. Amer. Chem. Soc.* **59**, 328 (1937).

symétriques par rapport au plan $z = 0$, elles apportent donc des contributions opposées. Il en est de même pour les fonctions décrivant les liaisons avec les deux substituants identiques. La molécule est donc inactive.

II. *Molécules possédant plusieurs centres d'asymétrie*

Examinons d'abord le cas simple d'une molécule formée par la soudure de deux radicaux identiques:

Les atomes A sont centre d'asymétrie si leurs quatre substituants sont de nature différente.

Supposons d'abord que les trièdres $AB_1B_2B_3$ soient inverses. Les contributions des liaisons correspondantes AB_i sont opposées d'après ce que nous venons de voir plus haut puisqu'un déplacement peut les amener à être symétrique par rapport à un plan. D'autre part la fonction φ décrivant l'état fondamental de la liaison A—A satisfait à l'identité: $\varphi(r, z, \theta) = \varphi(r, -z, \theta + \beta)$ en choisissant comme origine des coordonnées le milieu du segment A—A. β est l'angle qui définit la position d'un groupement $AB_1B_2B_3$ par rapport à l'autre dans la rotation autour la liaison A—A. En développant la fonction φ on obtient:

$$\varphi(r, z, \theta) = \sum a_n(r, z) \cos [n\theta - \alpha_n(r, z)]$$

$$\frac{\partial \varphi}{\partial \theta}(r, z, \theta) = -\sum n a_n(r, z)[\sin n\theta - \alpha_n(r, z)]$$

$$\varphi(r, -z, \theta + \beta) = \sum a_n(r, -z) \cos [n\theta + n\beta - \alpha_n(r, -z)]$$

D'où l'on tire: $a_n(r, -z) = a_n(r, z)$

$$\alpha_n(r, -z) = \alpha_n(r, z) + n\beta$$

c'est-à-dire:

$$\frac{\partial \varphi(r, -z, \theta + \beta)}{\partial \theta} = -\sum n a_n(r, -z) \sin [n\theta + n\beta - \alpha_n(r, -z)]$$

$$= -\sum n a_n(r, z) \sin [n\theta - \alpha_n(r, z)] = \frac{\partial \varphi(r, z, \theta)}{\partial \theta}$$

Pour l'état excité φ^z:

$$\varphi^z(r, z, \theta) = -\varphi(r, -z, \theta + \beta)$$

d'où l'on déduit: $\int \varphi^z \frac{\partial \varphi}{\partial \theta} d\tau = 0$. La contribution de la liaison A—A est donc nulle. La molécule est inactive. On retrouve ainsi le résultat classique (ex: acide méso-tartrique inactif par nature). Mais il ne faut pas manquer de remarquer la précision supplémentaire apportée. Le pouvoir rotatoire est identiquement nul pour toutes les configurations de la molécule (β quelconque) même si elle ne posède pas de plan de symétrie au sens géométrique.

Supposons maintenant que les trièdres $AB_1B_2B_3$ soient superposables. Les contributions des liaisons homologues AB_i sont égales. La fonction q de la liaison A—A est telle que: $q(r, z, \theta) = q(r, -z, -\theta + \beta)$. Relation d'où l'on déduit:

$$\frac{\partial q(r, z, \theta)}{\partial \theta} = -\frac{\partial q(r, -z, -\theta + \beta)}{\partial \theta}$$

Mais $q^z(r, z, \theta) = -q^z(r, -z, -\theta + \beta)$. L'intégrale $\int q^z \frac{\partial q}{\partial \theta} d\tau$ n'est pas nulle. La molécule est active (ex: acide tartrique droit ou gauche).

Cas général

Si la molécule possède plusieurs centres d'asymétrie diversement substitués les résultats précédents se généralisent sans peine toujours en accord avec les propositions classiques. Une différence mérite cependant d'être signalée. On admet généralement que le pouvoir rotatoire est la somme des contributions des centres actifs, appelés parfois "rotophores," ce qui conduit à des règles d'additivité, assez grossièrement vérifiées d'ailleurs. Ici au contraire le pouvoir rotatoire apparait comme la somme des contributions des liaisons aboutissant à au moins un centre d'asymétrie. La règle d'additivité des activités des centres actifs n'est donc rigoureuse que dans le cas où ces centres ne sont pas chimiquement liés.

Cependant l'indépendance des fonctions décrivant les liaisons σ suffisamment lointaines permet d'intéressantes relations. Comme exemple nous citerons la règle d'Hudson.[13] Si l'on considère les épimères α et β des sucres, la différence entres les rotations moléculaires $\rho_\alpha - \rho_\beta$ est constante pour une configuration donnée de l'atome de carbone C_2 voisin du carbone C_1 responsable de l'isomérie $\alpha - \beta$. La chimie classique transcrit ce fait en disant que la contribution du carbone C_1 ne dépend pas de la configuration des atomes non adjacents. Pour nous cette règle a une autre origine puisque la rotation moléculaire est la somme des contributions des liaisons σ. Pour l'isomère α nous avons en supposant les liaisons indépendantes:

$$\rho_\alpha = A + \rho(C_1C_2) + \rho(C_1O) + \rho(C_1OH) + \rho(C_1H)$$

Pour l'isomère β:

$$\rho_\beta = A + \rho'(C_1C_2) - \rho(C_1O) - \rho(C_1OH) - \rho(C_1H)$$

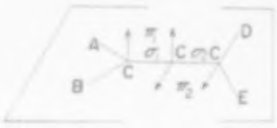
En effet les contributions des liaisons C_1O, C_1OH et C_1H sont opposées dans les deux isomères. D'autre part les contributions $\rho(C_1C_2)$ et $\rho'(C_1C_2)$ ne dépendent que de la configuration des atomes C_1 et C_2. La constante A fait intervenir les autres liaisons qui sont les mêmes pour les deux isomères. D'où l'on déduit que $\rho_\alpha - \rho_\beta$ ne dépend pas de la nature des substituants sur les atomes C_2, C_4, etc. . .

III. *Molécules actives ne possédant aucun centre d'asymétrie*

Pour certaines molécules on observe une activité optique bien qu'elles ne possèdent pas d'atomes asymétriques au sens classique. Nous examinerons quelques cas à la lumière de la théorie développée ici.

Carbures alléniques

Considérons une molécule d'allène tétrasubstitué disymétrique $\begin{matrix} A \\ B \end{matrix}\!\!>\!C\!=\!C\!=\!C\!<\!\!\begin{matrix} D \\ E \end{matrix}$. Elle est formée de liaisons σ entre les carbones et les divers substituants ABDE et de



liaisons doubles entre les carbones, constituées chacune par une liaison π, les plans de ces liaisons π étant perpendiculaires entre eux. La fonction π_1 n'est pas perturbée par les substituants A et B situés dans son plan nodal.[3] En revanche, elle est perturbée par les substituants D et E situés dans son plan principal. Il en résulte que la fonction π_1 ainsi que π_1^x excitée possèdent le plan (CDE) comme plan de symétrie mais que la densité électronique ne possède pas le plan (CAB) comme plan de symétrie puisque les substituants D et E sont différents. Il en est de même pour la fonction π_2 qui possède le plan (CAB) comme plan de symétrie mais dont la densité électronique ne possède pas le plan (CDE) comme plan de symétrie. La liaison σ_1 est perturbée par le fait que la densité des fonctions π_1 et π_2 ne sont pas respectivement symétriques par rapport aux plans (CAB) et (CDE). Si bien que σ_1 et σ_2 ne possèdent pas de plan de symétrie. D'autre part le moment $(\pi_1|\mathbf{R}|\pi_2^x)$ est nul. On en conclut à une contribution nulle pour les fonctions π_1 et π_2 qui possèdent chacune un plan de symétrie passant par la ligne des carbones selon laquelle sont orientés les moments de transition des fonctions π et que les transitions $\pi_1 \rightarrow \pi_j^x$ ont un moment nul. Mais l'absence de symétrie pour les fonctions σ_1 et σ_2 rend actives ces liaisons.

Si deux substituants, D et E par exemple, sont identiques, la densité π_1^2 possède le plan (ABC) comme plan de symétrie ainsi que la fonction σ_1. Il en est de même pour σ_2. La molécule est donc inactive.

Carbures aromatiques non plans

L'encombrement stérique vient souvent empêcher la planéité dans les molécules aromatiques, par exemple dans le 1.2 benzophénanthrène la présence de deux atomes d'hydrogène trop voisins provoque une torsion de la molécule qui prend une forme hélicoidale.[16] L'effet est encore plus marqué pour l'hexahélicène.[17] Les fonctions moléculaires décrivant les électrons π ou σ ne possèdent pas de plan de symétrie. Chaque liaison σ est donc active. D'autre part deux liaisons σ homologues, c'est-à-dire qui seraient symétriques si la molécule était plane, sont avec leurs quatre substituants superposables. Elles apportent donc des contributions deux à deux égales. La liaison centrale qui est son propre homologue apporte aussi une contribution non nulle. Pour les fonctions π qui apportent la contribution la plus importante dans le visible, il y a lieu de distinguer les transitions qui se font entre orbitales de même symétrie par rapport à l'axe z de torsion et celles entre orbitales de symétrie différente. Pour les premières le moment de transition (a|**R**|b) est porté par l'axe z. D'autre part la symétrie hélicoidale des fonctions d'onde se traduit par la relation: $F(r, z, \theta) =$

[16] F. H. Herbstein et G. M. J. Schmidt, *J. Chem. Soc.* 3314 (1954).
[17] M. S. Newmann et D. Lednicer, *J. Amer. Chem. Soc.* **78**, 4765 (1956).

$F(r, z, \theta + \pi)$ pour les orbitales "algébriquement" symétriques par rapport à z ou par $F(r, z, \theta) = -F(r, z, \theta + \pi)$ pour les antisymétriques. D'où l'on déduit pour ces fonctions respectives:

$$\frac{\partial F(r, z, \theta + \pi)}{\partial \theta} = \frac{\partial F(r, z, \theta)}{\partial \theta} \quad \text{et} \quad \frac{\partial F(r, z, \theta + \pi)}{\partial \theta} = -\frac{\partial F(r, z, \theta)}{\partial \theta}$$

Dans les deux cas les valeurs des quantités $q^x \frac{\partial q}{\partial \theta}$ sont deux à deux égales pour des éléments homologues par rapport à l'axe z. Les transitions entre orbitales de même symétrie sont donc actives. Pour les transitions entre orbitales de symétrie différente le moment $(a|\mathbf{R}|b)$ est perpendiculaire à l'axe z. Soit z' leur axe. Par rapport à z' on a pour les orbitales "algébriquement" symétriques par rapport à l'axe de torsion z:

$$F(r, z', \theta') = F(r, -z', -\theta') \quad \text{qui entraine:} \quad \frac{\partial F(r, -z', -\theta')}{\partial \theta'} = -\frac{\partial F(r, z', \theta')}{\partial \theta'}$$

et pour les antisymétriques:

$$F(r, z', \theta') = -F(r, -z', -\theta') \quad \text{et} \quad \frac{\partial F(r, -z', -\theta')}{\partial \theta'} = \frac{\partial F(r, z', \theta')}{\partial \theta'}$$

D'où il résulte que pour ces transitions entre orbitales de symétrie différente les éléments $q^x \frac{\partial q}{\partial \theta'}$ sont deux à deux égaux. Ces transitions sont donc aussi actives.

Se traite exactement de la même manière le cas des dérivés du diphényle pour lesquels l'impossibilité de rotation autour de la liaison médiane permet une séparation facile des deux isomères optiques.[18]

On voit donc que la méthode des orbitales moléculaires permet une intéressante approche du problème posé par le pouvoir rotatoire. Malheureusement les calculs développés ici ne permettent pas encore une évaluation numérique de la rotation moléculaire. Si nous avons pu remplacer les différences $\lambda_{k-1} - \lambda_{k+1}$ par $\varepsilon_{k+1} - \varepsilon_{k-1}$ le facteur de proportionnalité qui ne dépend que de l'atome central ne peut être actuellement évalué. En revanche, le calcul des intégrales s et σ ainsi que celui des termes I, réductibles à des intégrales de recouvrement, ne pose qu'une simple difficulté de calcul numérique. A ce stade la théorie permet donc en principe de déterminer à un facteur près l'activité optique pour un centre d'asymétrie donné, carbone par exemple.

[18] E. Wassermann, *Rev. Mod. Phys.* 32, 443 (1960).

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THE ANALYSIS OF MIXTURES OF OCTALINS

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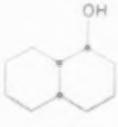
Abstract—A method of analysis is described, based on gas-liquid chromatography at moderate (ca. 2000 plates) efficiency on Apiezon L and benzyldiphenyl, whereby any octalin can be recognized. Any mixture of octalins can be tested for contamination by any bicyclo[5:3:0]decene by chromatography after hydrogenation. Quantitative analysis of binary mixtures of octalins is discussed; it is usually accurate, although an indirect method is necessary for mixtures of the $\Delta^{1,9}$- and *cis*-Δ^{1}-isomers.

IN order to study the effects of conformation on the pyrolysis of the diazodecalins, it was necessary to devise techniques for the quantitative analysis of the six isomeric octahydronaphthalenes ("octalins"). In earlier work by Hückel *et al.*, chemical degradation,[1] nitrosochloride formation,[2] and ultra-violet spectroscopy applied to the derived iodine complexes[3] have all been employed, while more recently gas-liquid chromatography has also been used.[4] For the sake of simplicity, we sought to rely exclusively on the last-mentioned technique, and have examined it systematically.

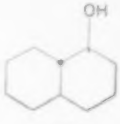
The six octalins were prepared by rational methods in the form of five different binary mixtures. Pyrolysis of the *cis*- and *trans*-β-decalol methylcarbonates, derived from the alcohols, m.p. 105° (I) and 75° (II) respectively, gave in each case a mixture of the Δ^{1}- and Δ^{2}-octalins. Pyrolysis of the methylcarbonates of the *cis*- and *trans*-α-decalols, m.p. 93° (III) and 63° (IV), gave similar binary mixtures, which this time had one component (clearly $\Delta^{1,9}$-octalin) in common.

I

II



III



IV

The other component was, in each case, identical chromatographically with one of the two pyrolysis products from the corresponding β-decalol; this was therefore the Δ^{1}-octalin, while the other pyrolysis product from the β-decalol ester must have been, in each case, the Δ^{2}-octalin. Finally, reduction of napthalene with lithium in liquid ammonia is known[5] to give Δ^{9}-octalin, with a little of the $\Delta^{1,9}$-isomer; in the mixture so obtained, one new product, the major component, was found, together with about 10 per cent of the $\Delta^{1,9}$-isomer, already recognized from the pyrolysis experiments. Thus every octalin could be identified with certainty, although no one isomer had been obtained pure.

[1] W. Hückel and H. Naab, *Liebigs Ann.* **502**, 136 (1933).
[2] W. Hückel, R. Danneel, A. Schwartz and A. Gercke, *Liebigs Ann.* **474**, 121 (1929).
[3] W. Hückel and O. Fechtig, *Chem. Ber.* **92**, 693, (1959).
[4] W. Hückel, R. Bross, O. Fechtig, H. Feltkamp, S. Geiger, M. Hanck, M. Heinzel, A. Hubele, J. Kurz, M. Maier, D. Maucher, G. Näher, R. Neidlein and R. B. Rashingkar, *Liebigs Ann.* **624**, 142 (1959).
[5] R. A. Benkeser, R. E. Robinson, D. M. Sauve and O. H. Thomas, *J. Amer. Chem. Soc.* **77**, 3230 (1955).

In any reaction involving the elimination of a functional group at the α-position in a decalin derivative, the possibility of rearrangement to a derivative of bicyclo[5,3,0]-decane has to be borne in mind. Analysis of mixtures of octalins, therefore, required a method of identifying the bicyclo[5,3,0]-decanes in the hydrogenation products. A mixture of the two forms (ratio 82:18) of this hydrocarbon was readily prepared by the hydrogenation of azulene in ethyl acetate; it is interesting that hydrogenation over platinum in acetic acid led to almost exclusive (ca. 98:2) formation of one component.

The retention times observed when a number of liquid phases were employed are listed in Table 1, together with values for naphthalene and tetralin. All are quoted ("R_D values") relative to *trans*-decalin = 100. With the apparatus available, the determination of R_D values for Apiezon L and benzyldiphenyl sufficed to identify any octalin, or to identify either of the perhydroazulenes in the presence of both decalins.

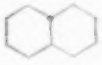
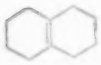
Quantitative analysis was attempted only for the five binary mixtures discussed above, and some favourable cases of more complex mixtures. It requires complete separation of the components and knowledge of the relationship between the area under the observed detector-response/time curve and the weight of material present. The first requirement involves the resolution of the column used; in the present work a difference in R_D values of about 7 per cent was called for, and the separation of $\Delta^{1,9}$- and *cis*-Δ^1-octalins was therefore impossible with any of the liquid phases investigated. The separation of *trans*-Δ^1- and -Δ^2-octalins was incomplete, even on Apiezon L, so that only an approximate value could be given for the relative peak areas; it should, however, be reliable to ±5 per cent. The other three mixtures were completely separated on one or other of the chosen stationary phases, and results should be reliable to ±2 per cent.

The detector used was of the flame ionisation type, and has recently been described.[6] While a linear relationship between weight and peak area has been claimed for a number of compounds,[7] it was necessary to test this for the substances under consideration. Accordingly, mixtures of *trans*-decalin with available binary octalin mixtures were prepared in a known weight ratio, and the signal areas compared. In all cases, the ratios were identical to within 2·5 per cent.

There remained the problem of analysing mixtures of *cis*-Δ^1-octalin and $\Delta^{1,9}$-octalin, which were inseparable, though not indistinguishable, on any of the columns used. It seemed that preferential isomerization of the trisubstituted olefine to an equilibrium mixture of this with the Δ^9-isomer might provide a solution; indeed, mixtures containing $\Delta^{1,9}$-octalin sometimes showed a peak corresponding to Δ^9-octalin, presumably formed by catalysis by adventitious acidic contaminants. Various isomerizing agents were investigated, using for convenience a mixture of *trans*-Δ^1- and $\Delta^{1,9}$-octalins. This mixture could be analysed directly, so that the unreactivity of the disubstituted olefine could be checked simultaneously. The results were of considerable interest and will be published in detail later; but for the present purpose a solution of perchloric acid (0·25 M) in acetic acid proved to be one of the most selective and convenient reagents examined. It gave a mixture which after reaction-times of between 1 and 100 minutes at 30° remained constant (within a range

[6] I. G. McWilliam and R. E. Dewar, *Nature Lond.* **181**, 760, (1958).
[7] I. G. McWilliam and R. A. Dewar, *Gas Chromatography* p. 142. Butterworths, London (1958).

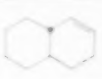
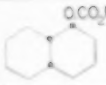
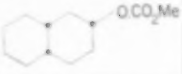
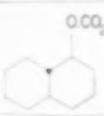
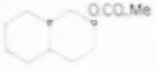
TABLE 1. RELATIVE RETENTION TIMES

Stationary Phase	Apiezon L	Squalene	Dinonyl Phthalate	Benzyl Diphenyl	Tricresyl Phosphate	$AgNO_3$/poly-ethylene glycol
Column Length	400 cm	260 cm	170 cm	250 cm	200 cm	250 cm
Column Temperature	120°	100°	100°	90°	100°	40°
	100	100	100	100	100	100
	105	102	110	132	133	155
	111	107	110	137	140	177
	125	130	130	144	144	155
	120	119	127	160	159	210
	125	126	136	179	178	235
	117	119	127	161	157	200
	124	135	145	192	182	240
	177			430		
	217			680		
	120 124			133 164		

of 2 per cent) containing as much *trans*-Δ^1-octalin as was originally present and Δ^9- and $\Delta^{1,9}$-octalins in a ratio of 9:1, evidently the equilibrium proportions.

When the same analytical procedure was applied to the mixture of *cis*-Δ^1- and $\Delta^{1,9}$-octalins a mixture of Δ^9-octalin and (*cis*-Δ^1 + $\Delta^{1,9}$)-octalins was formed for

TABLE 2. PRODUCTS OF THE PYROLYSIS OF THE DECALOL METHYL CARBONATES

					
	25%	75%			
		52%	48%		
	59%			41%	
				55%	45%

which the relative areas of the two peaks obtained remained constant, within 2 per cent, after reaction-times of between 1 and 30 minutes. This was taken to imply that the conversion of the *cis*-Δ^1-octalin to the equilibrium mixture, though undoubtedly faster than that of the *trans*-Δ^1-octalin (cf. the stabilities of the *cis*- and *trans*-decalins[8]), was still much slower than the interconversion of the $\Delta^{1,9}$- and Δ^9-isomers. It was then a simple matter to subtract 11 per cent of the Δ^9-octalin peak (the equilibrium amount of $\Delta^{1,9}$-octalin present) from the ($\Delta^{1,9}$- + *cis*-Δ^1-) octalin peak, and thus obtain the amount of *cis*-Δ^1-octalin finally (and originally) present in the mixture.

With the reservations made, the methods described should be useful in the study of the conformational requirements of various reactions. Indeed, the pyrolysis of the methylcarbonates of four of the decalols, as described above, provides an example; the results are listed in Table 2. In general, these results are consistent with earlier discussions.[9] The formation of as much as 25 per cent of $\Delta^{1,9}$-octalin from the ester of the alcohol (III) underlines the real possibility of *trans*- (presumably di-equatorial) elimination[10] in ester pyrolyses.

EXPERIMENTAL

To eliminate the effects of minor variations in temperature, column packing, etc., it is convenient to use an internal standard, and for the present purpose, *trans*-decalin was preferred. All retention times were expressed as relative to that of *trans*-decalin, taken as 100, and are denoted as R_D values. When these were close to 100, it was necessary to use *trans*-decalin before and after the sample injection

[8] N. L. Allinger and J. L. Coke, *J. Amer. Chem. Soc.* **81**, 4080 (1959).
[9] *inter alia* see D. H. Froemsdorf, C. H. Collins, G. S. Hammond and C. H. De Puy, *J. Amer. Chem. Soc.* **81**, 643 (1959); W. J. Bailey and W. F. Hale, *Ibid.* **81**, 647 (1959).
[10] F. G. Bordwell and P. S. Landis, *J. Amer. Chem. Soc.* **80**, 2450 (1958).

rather than as an internal label; such chromatographic runs were accepted only when the retention times of *trans*-decalin differed by less than 2%.

The following columns were employed: Apiezon L (a high-vacuum grease composed of aliphatic hydrocarbons, 400 cm); squalane (260 cm); dinonyl phthalate (170 cm); benzyldiphenyl (250 cm); tricresyl phosphate (200 cm); and silver nitrate (13%) in polyethylene glycol (250 cm). The R_D values obtained on these columns are summarized in Table 1.

The first two stationary phases were similar in behaviour; benzyldiphenyl and tricresyl phosphate were also similar to each other. Dinonyl phthalate was intermediate between the essentially aliphatic and the essentially aromatic solvents, as expected, and showed no advantages. The silver nitrate column showed remarkable behaviour; generally, it lowered the stability of the detector, and it gave retention times which depended upon the other components present, and peaks of unpredictable widths. To avoid the need for many control experiments, we abandoned its use. Apiezon L and benzyldiphenyl were chosen as standard stationary phases; neither was adequate in itself for identifying the six octalins when used under the conditions employed, as R_D values differing by 1–2% cannot be distinguished with certainty.

In all quantitative analyses two samples were examined and gave peak-area ratios and relative retention times constant to ±2%. Minor constituents amounting to 1% were readily identified. In any work with octalins it is necessary to examine samples immediately after preparation, to avoid loss, not necessarily at the same rate for all components, due to autoxidation.

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VOL. 12 1961

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THE DECOMPOSITION OF SULPHONYLHYDRAZONE SALTS: MECHANISM AND STEREOCHEMISTRY—II

THE PYROLYSIS OF THE DIAZODECALINS

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(*Received* 16 *September* 1960)

Abstract—Sulphonylhydrazones have been prepared from the four decalones and decomposed under conditions favouring the pyrolysis of the intermediate diazodecalins (a) as such and (b) after initial C-protonation. Mixtures of octalins were formed exclusively in each case. Quantitative analysis indicated that in the uncatalysed decomposition of the diazo-compounds the migration of an adjacent proton took place from a position antiparallel to that of the expelled nitrogen molecule. This implies that *free* carbenes are not intermediates in these reactions.

IN Part I of the present Series[1] it was shown that decomposition of sulphonylhydrazones under alkaline conditions involves a rate-determining, unimolecular elimination of sulphinate anion from the conjugate base to give the diazo-compound. This can decompose either directly or, in proton rich solvents, by initial C-protonation to a diazonium ion which then undergoes the expected substitution and elimination reactions. In a brief note submitted shortly after our paper, Friedman and Shechter[2] came to essentially similar conclusions. The direct decomposition of the diazo-compound, called "carbenoid decomposition" by Friedman and Shechter[2], is of course the more novel reaction. To clarify its mechanism we have prepared and decomposed *in situ* the four diazodecalins, using the sodium-acetamide reagent previously described[1] and the four decalone methanesulphonylhydrazones as progenitors.

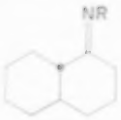
The mixtures of hydrocarbons obtained from the methanesulphonylhydrazones in a solution of sodium in acetamide at 156° were analysed by gas-chromatography, as described in the previous paper.[3] In no case was any hydrocarbon formed (>1 per cent yield) which could not be identified as one of the octalins; almost certainly a cyclodecalin, formed by intramolecular insertion,[2] would have had a markedly different R_p value from the olefines and would have been observed as such. On hydrogenation it would almost certainly have given, at least as a minor product, some hydrocarbon other than a decalin—if, indeed, it reacted at all. No products, other than *cis* and *trans* decalins, were in fact detected (>1 per cent) in the hydrogenation products; thus olefines possessing the skeleton of bicyclo-[5:3:0]-decane, which might have been formed by carbon participation in the decomposition of the 1-diazodecalins, were also absent.[3]

These results, and those reported by the American workers for 2-diazobutane,[2] imply that "intramolecular insertion" is essentially a reaction of *primary* diazo-compounds, decomposition to an olefine by hydrogen migration taking place without

[1] J. W. Powell and M. C. Whiting, *Tetrahedron* **7**, 305 (1959).
[2] L. Friedman and H. Shechter, *J. Amer. Chem. Soc.* **81**, 5512 (1959).
[3] J. W. Powell and M. C. Whiting, *Tetrahedron* **12**, 163 (1961).

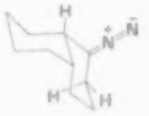
complications at least with simple secondary diazo-alkanes or -cycloalkanes. The proportions of the two isomers formed in each pyrolysis are indicated in Table 1. With one exception, they are consistent with the view[2] that a carbene is formed first and then rearranges to an olefine. One would predict in these circumstances that the product would be a statistical mixture of olefines, modified in the direction of an increased proportion of the more stable compound. It is to be expected that $\Delta^{1,9}$-octalin would be more stable than *trans*-Δ^{1}-octalin (and this is in fact true[4]); it is

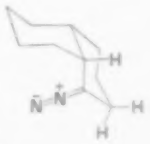
TABLE 1. PRODUCTS OF THE ALKALINE DECOMPOSITION OF THE DECALONE METHANESULPHONYLHYDRAZONES

Decalone Methane-sulphonyl-hydrazone	Reagent					
	A G	25% 27%	75% 73%			
	A G		51% 48%	49% 52%		
	A G	74% 82%			26% 18%	
	A G				35% 45%	65% 55%

=NR is $=N.NH.SO_2.CH_3$, giving $=N^+=N^-$
Reagent A: 1·3 N solution of sodium in acetamide, at 156°.
Reagent G: 1·3 N solution of sodium in ethylene glycol, at 156°.

entirely plausible that *trans*-Δ^{2}-octalin should be slightly more stable than *trans*-Δ^{1}-octalin, and that there should be no significant difference in stability between *cis*-Δ^{1}- and *cis*-Δ^{2}-octalins.[5] The analysis of the products from 1-diazo-*cis*-decalin, however, suggests a different explanation for all these results, as *cis*-Δ^{1}-octalin predominates over $\Delta^{1,9}$-octalin although the latter would be expected to be, and in fact is,[4] the more stable hydrocarbon. In 1-diazo-*cis*-decalin, two conformations, I and II, exist; the





[4] J. W. Powell and M. C. Whiting, *Proc. Chem. Soc.* In press.
[5] R. B. Turner, W. R. Meador and R. E. Winkler, *J. Amer. Chem. Soc.* 79, 4122 (1957).

first should be the more stable and, having the polar diazo-group exposed, might be more effectively solvated in acetamide and so able to react more rapidly. If it is assumed that the migrating hydrogen atom moves, from an axial position approximately antiparallel with the breaking C═N_2 bond, synchronously with the fission of the latter, then conformation I could give only *cis*-Δ^1-octalin while conformation II would probably give *cis*-Δ^1-and $\Delta^{1,9}$-octalins in about the same proportions as does 1-diazo-*trans*-decalin in giving *trans*-Δ^1- and $\Delta^{1,9}$-octalins. A 2:1-predominance of conformation I in the reaction, plus the above stereo-electronic hypothesis, would explain the results obtained with 1-diazo-*cis*-decalin. This hypothesis would also explain, as well as the free carbene hypothesis, the results obtained with the other diazodecalins, as in these cases there are no stereoelectronic restrictions and energetic factors would determine the products.

The view that secondary diazo-compounds decompose when possible by a synchronous mechanism might also account for some of the results reported by Friedman and Shechter,[2] notably the wide spacing (67:28:5) in the proportions of *trans*-Δ^2-, *cis*-Δ^2-, and Δ^1-butenes obtained from 2-diazobutanes. These are very different from typical reaction-product ratios obtained in the reactions of carbene itself.[6] Generalization of our results to acyclic systems would, however, be premature.

The decomposition reactions of the decalone sulphonylhydrazones were also carried out under Bamford–Stevens conditions, i.e. with the sodium derivative of ethylene glycol in excess of glycol.[7] The olefinic products did not differ greatly in composition from those obtained in acetamide, although in the preparative runs the total yields of olefines were only 30–40 per cent as against ca. 70 per cent in acetamide. The β-hydroxyethyl ethers were formed in ca. 30 per cent yield, whereas in acetamide no substitution products could be detected; this agrees with our earlier observations.[1] Probably the diazodecalins decompose in glycol mainly by the proton-catalysed route; equatorial diazonium cations would then be expected[8,10] to give, at least very largely, equatorial substitution products, while axial diazonium ions would mainly undergo diaxial 1:2-elimination, giving mixtures of olefines quite similar to those obtained from the similarly stereospecific decompositions of the diazo-compounds themselves, as observed in acetamide.

"The reaction of *p*-toluenesulphonhydrazones with base" was recently criticized as a method of preparing olefines by DePuy and Froemsdorf[9] on the grounds of low total yield and the formation of rearrangement products. These criticisms are justified as applied to the reaction in ethylene glycol,[7] the only solvent used by these workers; they are not justified if applied to the reaction in acetamide,[1] which is convenient and gives good yields of olefine-mixtures similar to those obtained, less conveniently except perhaps on a very large scale, by the pyrolysis of esters of the corresponding secondary alcohols.

EXPERIMENTAL

The preparation of the α-decalols and of the *cis*-β-decalol from commercial α- and β- naphthols by literature methods proved difficult, apparently because of catalyst poisons, possibly hydroxybenzthiophenes, in the latter. A standardized purification procedure was evolved: the naphthol was first

[6] W. von E. Doering, R. G. Buttery, R. G. Laughlin and N. Chaudhuri, *J. Amer. Chem. Soc.* **78**, 3224 (1956); cf. H. M. Frey, *Ibid.* **80**, 5005 (1957).
[7] W. R. Bamford and T. S. Stevens, *J. Chem. Soc.* 4735 (1952).
[8] J. A. Mills, *J. Chem. Soc.* 260 (1953); A. K. Bose, *Experientia*, **9**, 256 (1953).
[9] C. H. DePuy and D. H. Froemsdorf, *J. Amer. Chem. Soc.* **82**, 634 (1960).
[10] W. G. Dauben, R. C. Tweit and C. Mannerskantz, *J. Amer. Chem. Soc.* **76**, 4420 (1954).

distilled at atm press, then heated under reflux with Raney nickel (0·1 part) in ethanol (2 parts) for several hours, when a very dark solution was obtained. Filtration, removal of solvent and redistillation gave a specimen of naphthol with a reasonably high and reproducible rate of hydrogenation.

cis-β-Decalone methanesulphonylhydrazone

cis, cis-β-Decalol[10] (5 g) in acetone[11] (100 ml) was treated with a solution of chromic acid (6 N) in sulphuric acid (12 N) with external water-cooling until a strong yellow colour persisted in the acetone layer. After 15 min, water (500 ml) was added and the ketone was isolated with ether; without purification, it was dissolved in ethanol (5 ml) and added to a solution of methanesulphonylhydrazine (3·7 g) in ethanol at 60°. After 14 hr at 20° the product (5·65 g, 69%) separated, m.p. 99–102°; recrystallization from ethanol gave the *hydrazone* as needles, m.p. 104–105° (Found: C, 54·05; H, 8·25; N, 11·5. $C_{11}H_{20}N_2O_2S$ requires: C, 54·1; H, 8·25; N, 11·5%).

cis-α-Decalone methanesulphonylhydrazone was prepared by a similar method from *cis, cis-α*-decalol[12] (1·15 g). The crude product, m.p. 156–158°, had an infra-red spectrum free from the characteristic bands of *trans*-α-decalone methanesulphonylhydrazone at 1203, 1053 and 1029 cm^{-1}. On crystallization from 2-methoxyethanol, the temp being kept below 100°, it gave the desired *hydrazone* (4·5 g, 55%), m.p. 165·5° (Found: C, 54·2; H, 7·9; N, 11·64%).

trans-*β-Decalone methanesulphonylhydrazone*

$\Delta^{1,9}$-2-Octalone was prepared in 30% yield by condensation[13] of cyclohexanone (196 g) with methyl vinyl ketone (70 g) at 0° in the presence of benzyltrimethylammonium hydroxide (6 g). The product, b.p. 90–95°/1 mm, n_D^{20} 1·5262 (40 g) was reduced[14] with lithium (10 g) in liquid ammonia (1 l.) and ether (200 ml), giving material which showed an infra-red band of appreciable intensity at 1660 cm^{-1} as well as a stronger band at 1700 cm^{-1}. It was again reduced, lithium (ca. 4 g) being added to a solution in ammonia (750 ml) and ether (100 ml) until a deep blue colour persisted. After a further 10 min the product was isolated and distilled; it (20·8 g) had b.p. 65–68°/0·8 mm, n_D^{22} 1·4830 (Hückel[15] gives n_D^{18} 1·4809), and showed infra-red bands indicating the presence of a trace of the αβ-unsaturated ketone, as well as appreciable amounts of hydroxylic material. This crude ketone (5 g) was converted to the methanesulphonylhydrazone as described above; crystallization was not immediate, but the separated *hydrazone* (6·25 g, 78%) had m.p. 123°, unchanged on recrystallization (Found: C, 53·7; H, 7·9; N, 11·85%).

trans-α-*Decalone methanesulphonylhydrazone*

(a) Hydrogenation of purified α-naphthol (75 g) in ethanol (50 ml) over W-7 Raney nickel at 145° and 145 atm was complete after 8 hr. Filtration and distillation gave a fraction, b.p. 120–125°/14 mm, n_D^{25} 1·500 (38·4 g) consisting of a mixture of α-decalols. This was dissolved in acetone (200 ml) and treated with chromic acid solution (60 ml) as described above. The mixture of α-decalones obtained on isolation was equilibrated by heating under reflux with sodium hydroxide (33 g) in water (50 ml) and methanol (70 ml) for 18 hr. Isolation and distillation through a 20 cm Dufton column gave essentially pure *trans*-α-decalone (27·7 g), b.p. 112–113°/15 mm, n_D^{25} 1·4850, which largely crystallized on standing (Gutsche and Peter[12] give n_D^{20} 1·4852 (supercooled), b.p. 58°/0·8 mm, m.p. 31°). This material (15·4 g) in ethanol (25 ml) was added to methanesulphonylhydrazine (11 g) in hot ethanol (75 ml) and the solid which separated on cooling was recrystallized from β-methoxyethanol below 100°. The *hydrazone* (17·3 g, 51% from the α-decalol mixture) had m.p. 181–182° (Found: C, 54·5; H, 8·3; N, 11·6%).

(b) The crude α-decalone mixture obtained by oxidation (9 g) was added to methanesulphonylhydrazine (6·5 g) in hot ethanol (45 ml). A solid separated on cooling which, from its infra-red spectrum, was a mixture of the *cis*- and *trans*-α-decalone derivatives. It was heated under reflux for 3 hr in ethyl acetate (200 ml) and acetic acid (10 ml); on cooling the *trans*-α-decalone derivative (7·65 g, 54% from the decalol mixture) separated, m.p. 180–181°.

[11] cf. K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946).
[12] C. D. Gutsche and H. H. Peter, *J. Amer. Chem. Soc.* **77**, 5971 (1955).
[13] E. E. van Tamelen, personal communication.
[14] E. E. van Tamelen and W. C. Proost, *J. Amer. Chem. Soc.* **76**, 3632 (1954).
[15] W. Hückel, *Liebigs Ann.* **444**, 1 (1925).

Decomposition of the decalone methanesulphonylhydrazones

The methanesulphonylhydrazone (0·4 g) was added to a solution of sodium (0·15 g) in the appropriate solvent (5 g) (in the case of acetamide, dissolution of the sodium was carried out *in vacuo* to avoid combustion). The mixture was heated at 156° in a vapour-bath until nitrogen evolution slackened. Water (5 ml) was added while the reaction mixture was still warm, and the product was extracted into light petroleum (b.p. 60–80°, 1·5 ml). This extract was used directly for gas-liquid chromatography, after the addition of *trans*-decalin as internal indicator in appropriate cases.

The following is a typical preparative run, using the glycol reagent: *trans*-α-Decalone methanesulphonylhydrazone (5 g) was added to a solution of sodium (1·5 g) in ethylene glycol (50 ml). The mixture was heated to 155–160° until nitrogen evolution slackened (15 min). After cooling, water (100 ml) was added, and the product was extracted into ether (50 + 3 × 25 ml). The combined extracts were washed with water (4 × 25 ml), dried (magnesium sulphate), and the solvent was removed through a short column. The resulting oil was then distilled under reduced press, the fractions being obtained:

Fraction A B.p. 67–71°/7 mm, 1·00 g, n_D^{20} 1·4835.

Fraction B B.p. 85–87°/0·02 mm, 1·41 g, n_D^{20} 1·4871.

Fraction A was shown, by infra-red spectroscopy and gas-liquid chromatography, to be a mixture of $\Delta^{1,9}$-and *trans*-Δ^{1}-octalins, whilst the infra-red spectrum of fraction B showed it to be a hydroxyether, presumably 1-(β-hydroxyethoxy)-*trans*-decalin.

The results of this reaction, and the other preparative reactions which were carried out on the decalone methanesulphonylhydrazones, are summarized in the following table.

TABLE 2. PREPARATIVE REACTIONS ON THE DECALONE METHANESULPHONYLHYDRAZONES

Sulphonyl-hydrazone	Reagent	Olefine		Hydroxyether	
		Yield	Refractive index	Yield	Refractive index
cis-α	Acetamide	67%	1·4943 (18°)		
cis-α	Glycol	26	1·4925 (20°)	35%	1·4939 (20°)
trans-α	Acetamide	72	1·4933 (20°)		
trans-α	Glycol	36	1·4933 (20°)	34	1·4871 (20°)
cis-β	Glycol	43	1·4938 (17°)	29	1·4966 (17°)

A portion of the hydroxyether from the *cis*-β-hydrazone, after redistillation, was submitted for analysis, with the following result: (Found: C, 73·4; H, 10·9% $C_{12}H_{22}O_2$ requires: C, 72·7; H, 11·2%).

Acknowledgement—One of us (J. W. P.) thanks the Department of Scientific and Industrial Research for a research scholarship.

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VOL. 12 1961

CHEMICAL INVESTIGATION OF INDIAN LICHENS—XXIV*

THE CHEMICAL COMPONENTS OF *ALECTORIA VIRENS* TAYL. CONSTITUTION OF A NEW DEPSIDONE, VIRENSIC ACID

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(*Received* 3 *October* 1960)

Abstract—The Himalayan lichen *Alectoria virens* Tayl. is found to contain besides D-arabitol, the unusual association of vulpinic acid and a new depsidone, virensic acid, whose structure is established as IIa.

ALECTORIA VIRENS TAYL. is a rare lichen, a sample of which was collected during a special expedition to the Himalayan lake Roopkund. The lichen resembles *Usnea pectinata* Tayl. but differs from it in possessing a yellowish green colour. The quantity of the lichen collected was only 90 g but it provided enough material for a detailed examination. Light petroleum extract yielded vulpinic acid.[1] A subsequent ether extraction gave a new depsidone 'virensic acid'. The residual lichen on acetone extraction yielded D-arabitol.

Asahina[2] examined by paper chromatography as well as by microchemical methods, a sample of *A. virens* Tayl. and identified the colouring matter as vulpinic acid. More recently Dhar *et al.*[3], reported that a sample obtained from Chakrata area contained atranorin and psoromic acid. In view of the present work the sample from Chakrata was re-examined and found to contain only vulpinic acid and virensic acid; hence the earlier report was an error. Based on the present work *Alectoria virens* seems to be so far the only species of *Alectoria* containing vulpinic acid and it contains this acid in association with a depsidone virensic acid.

Virensic acid is a colourless, optically inactive compound, m.p. 245–246°, and has the molecular formula $C_{18}H_{14}O_8$. It contained no methoxyl group, two hydroxyl groups, one aldehyde group and one free carboxyl group. It readily formed a monomethyl ester, a dimethyl ether methyl ester, a mono anil, a mono dinitrophenylhydrazone. It was unaffected by boiling with methanol during 18 hours which ruled out the possibility of its being a depside. It was hydrolysed by aqueous alkali to a dicarboxylic acid which has the molecular formula $C_{18}H_{16}O_9$. The dimethyl ether methyl ester on treatment with methanolic potash formed a new compound which contained one more methoxyl group and was soluble in aqueous alkali indicating that virensic acid is a depsidone. The ultra-violet spectrum [λ_{max}^{MeOH} 240, 308 mμ (log ϵ 4·47, 3·68) and λ_{min} 225, 285 mμ (log ϵ 4·34, 3·48)] and the infra-red spectrum (ester C=O band at 1725 cm^{-1}) also confirmed the presence of a depsidone system in virensic acid.

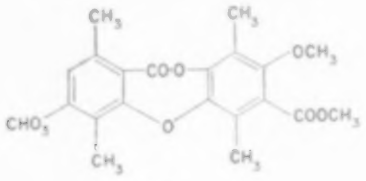
* Part XXIII: *J. Sci. Industr. Res. India* **18B**, 238 (1959).

[1] Y. Asahina and S. Shibata, *Chemistry of Lichen Substances* p. 43. Japan Society for the Promotion of Science, Tokyo (1954).

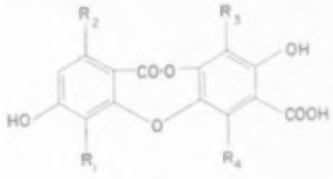
[2] Y. Asahina, *Fauna and Flora of Nepal Himalayas* (Edited by H. Kihara) p. 62. Fauna and Flora Research Society, Kyoto University, Japan (1955).

[3] M. L. Dhar, S. Neelakantan, S. Ramanujam and T. R. Seshadri, *J. Sci. Industr. Res. India* **18B**, 111 (1959).

Catalytic hydrogenation of virensic acid led to the up-take of 2 moles of hydrogen. That the absorption of hydrogen was solely due to the reduction of the —CHO group to the $—CH_3$ group was shown by the failure of the reduction product to exhibit carbonyl function and also by the infra-red spectrum. The reduction product produced a purple-red colour with alkali. This colour reaction is somewhat parallel to the behaviour of hypothamnolic acid[4] obtained by the reduction of thamnolic acid and may have significance. Complete methylation of the reduction product yielded a dimethyl ether methyl ester which was found to be identical with hypoprotocetraric acid methyl ether methyl ester (I) reported earlier.[5] Direct comparison was also effected with an authentic sample kindly furnished by Prof. Shibata, using mixed m.p., ultra-violet and infra-red spectra. Consequently the basic skeleton of virensic acid should have the structure II in which one of the substituents is a formyl group and the others are methyl groups. There are four possibilities (IIa, b, c, or d).



I



II

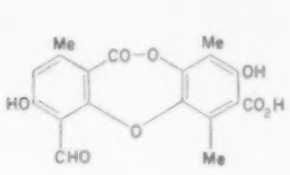
a, R_1 = CHO, R_2 = R_3 = R_4 = CH_3
b, R_2 = CHO, R_1 = R_3 = R_4 = CH_3
c, R_3 = CHO, R_1 = R_2 = R_4 = CH_3
d, R_4 = CHO, R_1 = R_2 = R_3 = CH_3

The correct structure (III) was deduced for virensic acid based on the following considerations. The structure IId is eliminated because a formyl group in the position shown would not exist free and would be present as a lactol (cf. salazinic acid,[6] and stictic acid[7]) and this would show a band in the infra-red spectrum at 1754 cm^{-1} not found in the spectrum of virensic acid. Further, the lactol grouping would not readily be reduced catalytically. The structure IIb is eliminated for similar reasons since the dicarboxylic acid obtained by the opening of the lactone ring does not show the lactol absorption, and undergoes catalytic reduction easily as does the original compound. The structure IIc is ruled out since the dimethyl ether methyl ester of virensic acid after lactone ring opening does not show any colour with alcoholic ferric chloride. If R_3 were a CHO group, then under the above conditions a new *ortho* hydroxy carbonyl system would be formed which would give a characteristic colour with alcoholic ferric chloride. Further, the spectral data of the ether ester after lactone ring opening does not support the presence of an *ortho* hydroxy aldehyde group. Hence III provides the correct structural formula for virensic acid.

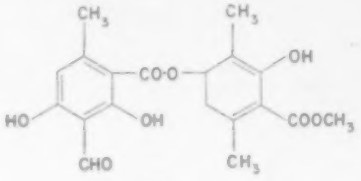
Virensic acid, as a depsidone has therefore a structure closely analogous to the depside atranorin (IV) which is common in the lichens. It is found in *Alectoria sulcata*

[4] Y. Asahina, F. Fuzikawa and M. Aoki, *Ber. Dtsch. Chem. Ges.* **74**, 928 (1941); Y. Asahina and T. Kusaka, *Ibid.* **69**, 450 and 1896 (1936).
[5] Y. Asahina and Y. Tanase, *Ber. Dtsch. Chem. Ges.* **67**, 414 and 716 (1934).
[6] Y. Asahina and S. Shibata, *Chemistry of Lichen Substances* p. 130. Japan Society for Promotion of Science, Tokyo (1954).
[7] Y. Asahina and S. Shibata, *Chemistry of Lichen Substances* p. 134. Japan Society for Promotion of Science Tokyo (1954).

Nyl.[8] but is absent in *A. virens*. Possibly virensic acid has taken its place owing to the presence in this species of the required oxidizing agent.



III



IV

EXPERIMENTAL*

Extraction of Alectoria virens *Tayl.*

(a) *With light petroleum* (*vulpinic acid*): The cut lichen (90 g) was extracted in a Soxhlet with light petroleum (b.p. 60–80°) for 24 hr. Evaporation of the extract left a solid residue (3·47 g) which on repeated crystallizations from benzene afforded yellow needles, m.p. 148–149°. The substance was identified as vulpinic acid; mixed m.p. with an authentic sample was not depressed and the ultra-violet and infra-red spectra of both the specimens were identical.

(b) *With ether* (*virensic acid*): The residual lichen was extracted with ether for 24 hr. A crystalline solid (4·3 g) separated out from the extract. Repeated crystallizations from dioxane–acetone gave *virensic acid* as colourless long needles, m.p. 245–247° (Found: C, 60·4; H, 4·4; OMe, nil; eq. wt. by lactone titration, 166·3 and 167·7; $C_{18}H_{14}O_8$ requires: C, 60·3; H, 3·9%; M.W. 358·3). Light absorption in methanol: λ_{max}: 240, 308 mμ (log ε 4·47, 3·68), λ_{min}: 225, 289 mμ (log ε 4·34, 3·48). Main I.R. bands: 3509–3333 (w), 2985 (m), 1724 (s), 1639 (s), 1613 (s), 1543 (m), 1422 (m), 1389 (m), 1348 (m), 1305 (w), 1266 (s), 1242 (m), 1198 (m), 1149 (s), 1121 (m), 1015 (w), 881 (w), 843–833 (w), 794 (w), 781 (w), 743 (m), 704 (w) cm^{-1}. Virensic acid gave a wine-red colour with alcoholic ferric chloride, a faint yellow colour with sodium hydroxide, violet colour changing to brown-red with conc sulphuric acid, and no colour with bleaching powder or conc nitric acid. It did not give the homofluorescein reaction. It formed a mono *dinitrophenylhydrazone*, which crystallized from acetone as orange rectangular plates, m.p. 256–258° (with sintering at 249°) (Found: C, 54·1; H, 3·1; $C_{24}H_{18}O_{11}N_4$ requires: C, 53·5; H, 3·4%). Virensic acid formed a mono *anil* which crystallized from acetone as golden yellow polygonal plates, m.p. 225–227° (Found: C, 66·3; H, 4·6; $C_{24}H_{19}O_7N$ requires: C, 66·5; H, 4·4%).

(c) *Extraction with acetone* (D-*arabitol*): The remaining lichen was extracted with acetone for 24 hr and the dark brown residue left on evaporation of the solvent was macerated with water and the insoluble portion filtered off. The aqueous extract on evaporation in a dessicator left a syrup which on trituration with methanol afforded a solid. It was recrystallized from methanol–ether mixture to yield D-arabitol, m.p. 99–102° (0·07 g); $[\alpha]_D^{26°}$ +7·35 (*c*, 0·07 in saturated aqueous borax). A mixed m.p. with an authentic sample showed no depression.

Methyl virensate

A solution of virensic acid (0·1 g) in dry acetone (25 ml) was heated with sodium hydrogen carbonate (0·15 g) and dimethyl sulphate (0·2 ml) for 8 hr. The sodium salts were filtered off and the filtrate on evaporation yielded a residue (0·08 g) of *methyl virensate*, which crystallized from ethyl acetate as colourless long flat needles, m.p. 215–216·5° (Found: C, 61·3; H 4·4; OMe 8·3; $C_{19}H_{16}O_8$ requires: C, 61·3; H, 4·3; 1 OMe, 8·3%). Light absorption in methanol: λ_{max} 243, 300, 316 mμ (log ε 4·49, 3·85, 3·78), λ_{min} 228, 294, 310 mμ (log ε 4·38, 3·70, 3·75). Main I.R. bands: 3390–3279 (w), 1724 (s), 1639 (s), 1600 (shoulder), 1563 (m), 1429 (m), 1408 (shoulder), 1372 (m), 1361 (shoulder), 1342 (shoulder), 1316 (s), 1282 (s), 1267 (s), 1250 (s), 1198 (s), 1172 (m), 1149 (s), 1124 (m), 1074 (m), 1022 (m), 971 (w), 855 (w), 796 (m), 763 (m) cm^{-1}. The ester gave a wine-red colour with alcoholic ferric chloride.

* All the I.R. spectra were taken in KBr disk unless otherwise stated.

[8] Y. Asahina and H. Hayashi, *J. Pharm. Soc, Japan* **48**, 1094 (1928).

Methyl virensate dimethyl ether

A solution of virensic acid (0·1 g) in dry acetone (25 ml) was heated with anhydrous potassium carbonate (2 g) and dimethyl sulphate (0·5 ml) for 18 hr. The product was crystallized from benzene–light petroleum and the *ether ester* was obtained as colourless fine needles m.p. 160–162° (Found: C, 62·6; H, 4·5; OMe, 23·4; $C_{21}H_{20}O_8$ requires: C, 63·0; H, 5·0; 3 OMe, 23·2%). Light absorption in methanol: λ_{max} 301, 316 mμ (log ε 3·57, 3·42), λ_{min} 294, 308 mμ (log ε 3·36, 3·26). Main I.R. bands: 2874 (w), 1709 (s), 1681 (m), 1587 (m), 1527 (m), 1451 (m), 1414 (m), 1399 (m), 1379 (m), 1368 (m), 1333 (m), 1274 (s), 1258 (shoulder), 1220 (shoulder), 1208 (m), 1190 (m), 1166 (w), 1140 (s), 1124 (m), 1087 (w), 1048 (w), 1029 (w), 990 (w), 962 (w), 909 (w), 855 (w), 793 (w), 769 (w) cm.$^{-1}$

Opening of the lactone ring of virensic acid

A solution of virensic acid (0·1 g) in 10% aqueous potassium hydroxide (2 ml) was kept at room temp for 1 hr. The solution was acidified and extracted with ether. The solid obtained from ether solution was crystallized from alcohol. The *diacid* was obtained as colourless rectangular prisms and needles, m.p. 216–217° (Found: C, 56·1; H, 4·4; $C_{18}H_{16}O_{9}\cdot\frac{1}{2}H_2O$ requires: C, 56·1; H, 4·4%). It gave a pinkish-brown colour with ferric chloride and a deep yellow colour with bleaching powder and with sodium hydroxide. Light absorption in methanol: λ_{max} 227, 270, 305 and inf. 333 mμ (log ε 4·50, 4·23, 3·72, and 3·54), λ_{min} 252, 300 mμ (log ε 4·09, 3·64). Main I.R. bands: 3448 (w), 2899 (w), 1681 (m), 1621 (s), 1431 (m), 1393 (shoulder), 1379 (m), 1342 (w), 1266 (s), 1220 (m), 1198 (m), 1176 (w), 1105 (m), 901 (w), 820 (w), 797 (w) cm^{-1}.

Opening of the lactone ring of methyl virensate dimethyl ether

Methyl virensate dimethyl ether (0·08 g) was mixed with methanolic potassium hydroxide (5 ml; 10%) and kept at room temp for 2½ hr. Acidification and extraction with ether followed by evaporation of ether from the extract gave a product which crystallized from ethyl acetate–light petroleum as colourless stout rectangular tablets, m.p. 134–135° (Found: C, 61·2; H, 5·8; OMe, 28·1; $C_{22}H_{24}O_9$ requires: C, 61·1; H, 5·6; 4 OMe, 28·7%). It did not give any colour with alcoholic ferric chloride. Light absorption in methanol: λ_{max} 226, 280, 305, 325 mμ (log ε 4·45, 3·84, 3·26, 3·19), λ_{min} 274, 298, 317 mμ (log ε 3·78, 3·18, 3·08). Main I.R. bands: 3448 (s), 2959 (m), 1718 (vs), 1667 (s), 1600 (s), 1553 (m), 1460 (s), 1399 (s), 1370 (shoulder), 1340 (m), 1316 (shoulder), 1282–1266 (s), 1242 (shoulder), 1205–1190 (s), 1170 (s), 1149 (s), 1111 (s), 1075 (m), 1053 (m), 1020 (shoulder), 1010 (m), 990 (m), 978 (m), 901 (m), 890 (m), 848 (m), 833 (m), 800 (w), 781 (w), 769 (w), 763 (w), 746 (w), 716 (w), 671 (w) cm^{-1}.

Catalytic reduction of virensic acid

A solution of virensic acid (0·1 g) in methanol (15 ml) was shaken with hydrogen in the presence of palladized charcoal (0·1 g, 10%) until no further absorption took place. During 2 hr hydrogen absorbed was 13·5 ml at 32·1° and 736·2 mm. The catalyst was removed by filtration and methanol evaporated *in vacuo*. The residue (0·06 g) crystallized from ethyl acetate as clusters of stout rectangular prisms, m.p. 240° (Found: C, 62·7; H, 5·0; $C_{18}H_{18}O_7$ requires: C, 62·8; H, 4·7%). It gave a violet colour with alkalis and alkali carbonates and a pale red colour with bleaching powder. Light absorption in methanol: λ_{max} 225, 265, 280 mμ (log ε 4·42, 4·08, 4·05), λ_{min} 245, 277 mμ (log ε 4·05, 3·98). Main I.R. bands: 3559 (m), 3226 (m), 3125 (m), 2899 (m), 2564–2326 (w), 1689 (s), 1626 (m), 1592 (s), 1550 (m), 1481 (m), 1439 (m), 1401 (m), 1370 (m), 1304 (s), 1258 (s), 1209 (m), 1149 (s), 1075 (m), 1042 (w), 1020 (w), 1009 (m), 893 (w), 855–840 (w), 803 (m), 784 (w), 752–735 (w), 714–704 (w) cm^{-1}.

Complete methylation of reduced virensic acid

A solution of the above compound (0·1 g) in methanol was treated with excess of diazomethane in ether and kept overnight in the refrigerator the unchanged diazomethane decomposed by acetic acid and the solvent removed *in vacuo*. The product crystallized from ethyl acetate as colourless stout rectangular tablets, m.p. 169–170°. It did not give any colour with alcoholic ferric chloride. A mixed m.p. with an authentic specimen of hypoprotocetraric acid methyl ether methyl ester was undepressed. The ultra-violet and the infra-red spectra of both the specimens were identical. Light absorption in

methanol: λ_{max} 269 mμ (log ϵ 3·99), λ_{min} 247 mμ (log ϵ 3·85), [authentic specimen had the absorption: λ_{max} 269 mμ (log ϵ 3·92), λ_{min} 245 mμ (log ϵ 3·68)]. Main I.R. bands: ($CHCl_3$) 2959 (m), 2890 (m), 1712 (s), 1592 (s), 1553 (m), 1447 (s), 1429 (shoulder), 1399 (s), 1333 (s), 1307 (m), 1274 (s), 1176 (m), 1130 (s), 1111 (m), 1083 (m), 1052 (m), 1030 (m), 1005 (m), 996 (m), 972 (m), 899 (w), 841 (w) cm^{-1}.

The same product was also obtained by the reduction of virensic acid dimethyl ether methyl ester (0·1 g) in methanol with hydrogen in the presence of palladized charcoal (0·1 g, 10%) and working up the product as usual.

Acknowledgements—Our thanks are due to Swami Pranavananda, F.R.G.S., of Holy Kailas and Manasarover, for the collection of this rare lichen during his expedition to Roopkund, to Dr. Awasthi for the identification of the lichen, to Prof. Shibata for a sample of hypoprotocetraric acid methyl ether methyl ester and to the Govt. of India for a Senior Research Fellowship to one of us (K. G. S.).

VOL.
12
1961

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TERPENOIDS—XXIV

ISOLATION OF 12-METHOXYDIHYDROCOSTUNOLIDE FROM COSTUS ROOT OIL*

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(*Received* 14 *October* 1960)

Abstract—The methoxylactone isolated from costus root oil is shown to be 12-methoxydihydrocostunolide.

THE lactone described in an earlier communication[1] is shown to have the structure I.

The lactone has the molecular formula $C_{16}H_{24}O_3$. One of the oxygen atoms is present as a —OMe group. The remaining two oxygen atoms are present in a γ-lactone function as revealed by I.R. spectrum (band at 1760 cm^{-1}). The I.R. spectrum also exhibits a band at 1660 cm^{-1} which taken together with the fact that no formaldehyde is formed on ozonolysis shows the presence of one or more trisubstituted double bonds. The U.V. spectrum of the methoxy lactone (I) is identical with the characteristic U.V. spectrum of dihydrocostunolide (II).[2] This suggests that like dihydrocostunolide, the methoxy lactone also contains a ten membered ring and two trisubstituted double bonds distributed in identical manner. In view of this it was felt that the methoxy lactone (I) must be represented by the partial structure III. This is confirmed by studying the ozonolysis products of the methoxy lactone. The acidic portion from its ozonolysis was esterified with diazomethane. The resulting material was shown to be a mixture of methyl levulinate and the ketoester (IV). The structure IV assigned to the latter ester is in agreement with its elemental analysis and I.R. spectrum.

While the methoxylactone may be isolated from the methanol-eluted portion during the chromatography of costus root oil, the earlier portions did not contain this lactone (I). In view of this and the experimental data described above, which suggests the partial formula III, it was suspected that the methoxylactone (I) may be an artifact formed from the interaction of methanol with costunolide (V), which is a major lactonic constituent of costus root oil.[1] The addition of methanol to α,β-unsaturated ketones and esters under slightly basic conditions, is well known.[3,4] This type of addition should furnish the methoxy lactone having the structure I from costunolide. To confirm this, costunolide was allowed to react with methanol in the presence of a trace of base. The methoxy lactone obtained by this reaction is identical with the methoxy lactone isolated from costus root oil.

The absolute configuration of the methoxylactone (I) follows from its partial synthesis from costunolide. The configuration at C_6 and C_7 must be the same as in

* Contribution No. 418 from the National Chemical Laboratory, Poona-8, India.

[1] A. Paul, A. S. Bawadekar, R. S. Joshi, G. H. Kulkarni, A. Somasekar Rao, G. R. Kelkar and S. C. Bhattacharyya, *Perf. and Ess. Oil Rec.* **51**, 115 (1960).

[2a] A. Somasekar Rao, G. R. Kelkar and S. C. Bhattacharyya, *Tetrahedron* **9**, 275 (1960); [b] J. W. Steele, J. B. Stenlake and W. D. Williams, *Chem. & Ind.* 1384 (1959).

[3] D. K. Fukushima and T. F. Gallagher, *J. Amer. Chem. Soc.* **73**, 196 (1951).

[4] C. F. Koelsch, *J. Amer. Chem. Soc.* **65**, 437 (1943).

costunolide.[3,5] The reaction leading to its formation from costunolide and methanol is expected to be reversible. Hence of the two C_{11} epimers, the thermodynamically more stable epimer should be formed. It is generally accepted[6] that in santonin and related compounds, for a transfused butanolide the more stable configuration is the one in which the 11-Me group is *trans* to the hydrogen atom at C_7. If the same

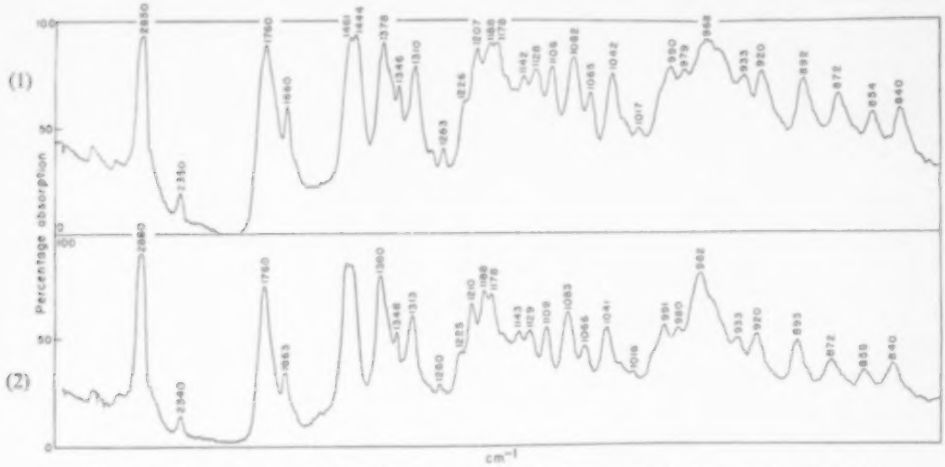
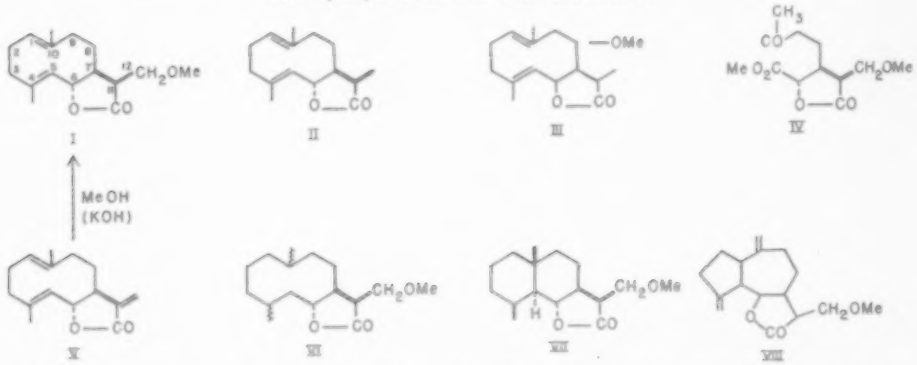


FIG. 1. Infra-red spectra (in Nujol) of (1) methoxydihydrocostunolide from costus oil and (2) methoxydihydrocostunolide from costunolide.



relation holds good in the costunolide series, the methoxy methylene group at C_{11} in the methoxy lactone (I) must be assigned the β-configuration.

The hydrogenation of the methoxy lactone (I) in acetic acid medium in the presence of platinum catalyst results in the consumption of slightly more than one mole of hydrogen. The product which by analogy with costunolide is expected to be a mixture of the lactones VI and VII yields 1-methyl-7-ethyl naphthalene on selenium dehydrogenation.

The addition of methanol to conjugated lactones like costunolide is expected to be general.* Because of the mild condition under which the addition takes place and also

* Mr Simonovitch, a guest worker in our laboratory has shown that dehydrocostus lactone also gives a methoxylactone (VIII), n_D^{25} 1·5231, $[\alpha]_D$ +19 (alchohol) under similar conditions.

[5] V. Herout and F. Sorm, *Chem. & Ind.* 1067 (1959).

[6] W. Cocker and T. B. H. McMurray, *Tetrahedron* **8**, 181 (1960).

the fairly good yield of the addition product, this reaction may be used for the detection of such unsaturated lactones. The blocking of such double bonds would lead to comparatively more stable products which may be very helpful for structural work.

EXPERIMENTAL

All melting points and boiling points are uncorrected. Rotations were taken in chloroform. Ultra-violet spectra were taken in 95% alcohol with Beckman DK-2 recording spectrophotometer. Elemental analysis were carried out by Mr. Pansare and his colleagues. Infra-red spectra were determined by Mr. Jose.

Isolation of methoxy dihydrocostunolide (I). Methanol faction "N" (100 g) of costus root oil[1] was chromatographed on acid washed neutral alumina (4 kg, Gr. III). The portion eluted by benzene and methanol was dissolved in ether and kept at −15° for 4 days. The solid (5 g) which separated out was crystallized twice from methanol to give needle shaped crystals m.p. 127–128°, $[\alpha]_D = +115°$ (*c*, 4·8). (Found: C, 72·76; H, 9·16; OMe, 11·1%. $C_{16}H_{24}O_3$ requires; C, 72·69; H, 9·19; OMe, 11·74%). U.V. spectrum; This was identical with that of dihydrocostunolide ε_{212} 8,800; ε_{220} 5900; ε_{230} 2400). I.R. spectrum (in Nujol), is reproduced in Fig. 1.

Hydrogenation of methoxydihydrocostunolide. Methoxydihydrocostunolide (I, 1 g) was hydrogenated in acetic acid at room temp and atm press in the presence of platinum oxide. The hydrogenation stopped after the uptake of slightly more than one mole of hydrogen. The product (VI and VII) was worked up in the usual way. It had b.p. 175°/0·3 mm (bath) n_D^{30} 1·4955; d_4^{30} 1·086; $[\alpha]_D^{30} = +33·5$ (*c*, 3·4) (Found: C, 71·6; H, 9·6, $C_{16}H_{26}O_3$ requires: C, 72·14; H, 9·84%, $C_{16}H_{28}O_3$ requires: C, 71·6; H, 10·52%).

Selenium dehydrogenation of the lactone mixture (VI *and* VII). The mixture of lactones (VI and VII, 0·75 g) was dehydrogenated with selenium powder (1·3 g) at 290–320° for 40 hr in an atm of nitrogen. The reaction product was distilled. The U.V. spectrum of the distillate (0·29 g) showed it to be predominately naphthalenic (maxima at 229, 281, 325 and 331 mμ, ε, 66,000; 3800; 330 and 140 respectively, assuming molecular weight to be 170). It was characterized as its s-trinitrobenzene complex m.p. and mixed m.p. with an authentic sample of T.N.B. complex of 1-methy-7-ethylnapthalene, 107° (Found: C, 58·61; H, 4·58; N, 10·52; $C_{19}H_{17}N_3O_6$ requires: C, 59·53; H, 4·47; N, 10·96%).

Ozonolysis of methoxydihydrocostunolide (I). A stream of ozonized oxygen was passed through an ice-cooled solution of methoxydihydrocostunolide (I) (0·44 g) in ethyl acetate (10 ml) till ozonolysis was complete. The solvent was removed at 50°; the pressure at the end was 2 mm. The residual material was decomposed by heating carefully with water on the bath for 2 hr, when a clear solution was obtained. An aliquot portion was utilized for the determination of number of methyl ketone groups[2] formed by ozonolysis (Found: number of methyl ketone group, 2·1; Calc. for the structure I, 2·0). The remaining portion (88% of the original quantity) was made alkaline. The non-acidic portion was removed by repeated extractions with ether. The alkaline layer was then made acidic with sulphuric acid and extracted repeatedly with ether. The ether extract was esterified with diazomethane. The mixture of esters on distillation furnished two fractions (i) b.p. 120–150°/40 mm (bath) (72 mg) (ii) b.p. 180–210°/0·8 mm) (bath) (0·15 g) (i) was identified as methyl levulinate[2] by its 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. with an authentic sample, 141–142° (Found: C, 46·67; H, 4·56; N, 18·05; $C_{13}H_{14}N_4O_6$ requires: C, 46·45; H, 4·55; N, 18·06%) (ii) is identical with IV (Found: C, 56·22, H, 6·7; $C_{12}H_{16}O_6$ requires: C, 55·80, H, 7·03%).

Conversion of costunolide to methoxydihydrocostunolide (I). To a solution of costunolide (V, 1·12 g) in methanol (30 ml) was added a methanolic solution of potassium hydroxide prepared from 1·1 g KOH, 3 ml water and 17 ml methanol. The mixture was kept at room temp for 60 hr diluted with water and extracted with ether. The ether extract furnished 0·65 g of a solid with U.V. spectrum almost identical with that of methoxydihydrocostunolide. Two recrystallizations from methanol gave pure methoxydihydrocostunolide (I) m.p. 126–127°, $[\alpha]_D = +111°$ (*c*,1·4). (Found: C, 73·4; H 9·6; OMe 10·7; $C_{16}H_{24}O_3$ requires: C, 72·69; H, 9·15; OMe 11·74%). The m.p. of the product was undepressed on admixture with the methoxy lactone isolated from costus root oil. The U.V. and I.R. spectra of the two samples were also identical.

[2] Heibron and Bunbrury, *Dictionary of Organic Compounds* Vol. 3, p. 178. (1953 edition).

Tetrahedron, 1961, Vol. 12, pp. 181 to 185. Pergamon Press, Inc. Printed in Northern Ireland

MALVIDIN 3-GALACTOSIDE AND DELPHINIDIN 7-GALACTOSIDE FROM *BLADHIA SIEBOLDII*

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Abstract—Two pigments have been isolated from the fruits of *Bladhia sieboldii* and their structures identified as malvidin 3-galactoside and a new pigment delphinidin 7-galactoside(bladhianin).

VOL. 12 1961

IN continuation of our work on natural anthocyanins[1] the pigments in the peel of *Bladhia sieboldii* have been investigated. About fifteen native species of *Bladhia* (Myrsinaceae) are found in Formosa. The fruits of *Bladhia sieboldii* change colour during ripening from pale yellow through pink, red and finally violet-black.

The crude pigment extract from ripe fruits showed, on paper chromatography, 3 pigment spots. Li and Wagenknecht[2] separated and purified two closely related anthocyanin pigments by metasilicic acid partition chromatography. Application of this method using silica gel finer than 200 mesh and various solvent systems did not effect separation of the pigments. On alumina column chromatography,[3] the alumina adsorbed the pigments so firmly that they were difficult to elute. In the present investigation a modified adsorption column chromatographic method involving silica has been devised for separation and purification of closely related anthocyanin pigments. Each of the three pigment fractions obtained by paper chromatography of the crude pigments, when further chromatographed on silica powder, gave four pigment zones indicating that there are no less than twelve kinds of anthocyanin pigments in the skins of *B. sieboldii*.

In order to obtain sufficient pure pigment to determine its structure, special methods were devised and two pigments termed "Anthocyanin A" and "bladhianin" were isolated.

Anthocyanin A does not contain an organic acid residue.[4] When hydrolysed with hydrochloric acid a violet-red anthocyanidin is produced. From the U.V. absorption spectra, qualitative tests[5] and paper chromatography the anthocyanidin was identified as malvidin chloride (I). The sugar in the hydrolysate of Anthocyanin A is galactose identified by comparison of the phenylosazone and paper chromatogram with authentic specimens. The quantitative hydrolysis shows that it is malvidin mono-galactoside and the position of galactose was fixed at position 3 since it is not attacked by ferric chloride.[6] Thus Anthocyanin A is identified as malvidin 3-galactoside. The distribution number[7] is $9{\cdot}0 \pm 0{\cdot}8$ which agrees with the value of 8·6 for primulin (malvidin 3-galactoside)[8] as well as with those found for monoglycosides (9·8 to 11·0).[7]

[1] P. Y. Yeh, W. F. Ling and R. Takasaka, *Science* **128**, 312 (1958).
[2] K. C. Li and A. C. Wagenknecht, *J. Amer. Chem. Soc.* **78**, 979 (1956).
[3] P. Karrer and F. W. Strong, *Helv. Chim. Acta* **19**, 25 (1935).
[4] K. Hayashi, *Experimental Methods in Plant Pigments* (in Japanese). Nakayama-Shoten, Tokyo (1954).
[5] G. R. Robinson and R. Robinson, *Biochem. J.* **25**, 1687 (1931).
[6] A. Leon, A. Robertson, R. Robinson and T. Seshadri, *J. Chem. Soc.* 2672 (1931).
[7] R. Willstätter and E. H. Zollinger, *Liebigs Ann.* **412**, 208 (1916).
[8] R.Scott-Moncrieff, *Biochem. J.* **24**, 767 (1930); A. Bell and R. Robinson, *J. Chem. Soc.* 813 (1934).

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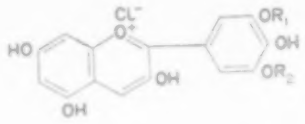
Diglycosides usually gave distribution numbers below 2·0.[7] The colour reactions of Anthocyanin A are also in good agreement with those reported for primulin.[8]



I: $R_1 = R = Me$
II: $R_1 = R_2 = H$
III: $R_1 = H$, $R_2 = Me$

Bladhianin forms a scarlet red picrate and does not contain an organic acid residue. It distribution number is 13 ± 0·8, which is much higher than that (eight) reported for delphinidin 3-galactoside.[9] Quantitative hydrolysis yields one mole each of delphinidin chloride (II) and galactose. The ferric chloride test indicates that the galactose is not at position 3. Therefore, it is a new anthocyanin with galactose in the 5 or 7 position.

Bladhianin was exhaustively methylated with dimethyl sulphate in aqueous alkaline solution with the formation of a chalcone. Since anthocyanidin methyl ether is not formed on acid hydrolysis of the chalcone,[6,10] the sugar residue is not attached to the 5 position and therefore the structure of bladhianin is delphinidin 7-galactoside. Although 3,7-diglucoside and 5,7-diglucoside of cyanidin chloride[11] and pelargonidin 7-β-glucoside chloride[6] were synthesized, bladhianin is the first natural anthocyanin bearing a sugar group on the 7-position.

It is of interest that malvidin 3-galactoside is found in the highest zone of the silica chromatogram obtained from the highest spot on the paper chromatogram of the crude pigments, and delphinidin 7-galactoside is found in the lowest zone of the silica chromatogram of the lowest spot on the paper chromatogram. As mono- or di-glucosides of malvidin (I), petunidin (III) and delphinidin(II) are found together in grape,[12] it is reasonable to presume the presence of galactosides of petunidin as well as other glycosides of malvidin, petunidin, and delphinidin in the skins of the fruits of *Bradhia sieboldii*.

EXPERIMENTAL

Silica powder and silica gel (granular) used were C.P. grades, Wako Chem. Co., Japan. Silica and silica gel, ground and screened with a 110 mesh sieve, were fractionated by sedimentation in water to remove the finer particles which retarded the flow of solvent in chromatography. The Spaeth and Rosenblatt's method[12] was modified as follows: Silica (or silica gel) powder (100 g) was stirred vigorously with distilled water (1300 ml) for ½ hr and kept undisturbed for 5 min. The supernatant mixture was decanted and was allowed to settle for 30 min. The first and second sediments were dried at 100–110° for 8 hr, the former was screened with a 200 mesh sieve and combined with the latter to use in chromatography.

The fruits (1 kg) were washed with water immediately after the collection and dried at room temp. The fruits were extracted 3 times, over a period of 9 days with ethanol containing 1% HCl in a refrigerator, to give 1 l. of combined extracts. The extracts gave, when chromatographed on Toyo filter paper No. 2, three spots, having R_f values 0·29 (the highest spot), 0·21 (middle spot) and 0·16 (the lowest spot), when developed with 4:1:1 BuOH–AcOH–H_2O and 0·59, 0·51, and 0·41 in 5:1:4 80% HCOOH–36% HCl–H_2O.

[9] K. Hayashi, G. Suzushino and K. Ouchi, *Proc. Japan. Acad* **27**, 430 (1951); *Chem. Abstr.* **46**, 7567g (1952).
[10] P. Karrer, *Helv. Chim. Acta* **10**, 750 (1927); **11**, 837 (1928); **12**, 292 (1929); C. G. Nordström, *Acta Chem. Scand.* **10**, 1491 (1956).
[11] R. H. MacDowell, R. Robinson and A. R. Todd, *J. Chem. Soc.* 806 (1934).
[12] E. C. Spaeth and D. H. Rosenblatt, *Analyt. Chem.* **22**, 1321 (1950).

A mixture of lead acetate (5 g) and yellow lead oxide (3 g) in water (6 ml) was shaken at room temp until white in colour. The mixture was kept at room temp overnight and the supernatant liquid, contained lead subacetate,[13] was diluted with an equal volume of ethanol. To 1 l. of the pigment extract, 50 ml of twice diluted lead subacetate solution was added, and the precipitate separated and dried (21 g). The paper chromatogram of the pigments obtained by decomposing the lead salts showed 3 spots, while that of the pigments in the mother liquor of the lead salts showed mainly one spot, the highest spot. The mother liquor was reserved for the isolation of Anthocyanin A.

Powdered lead salts (10 g) was mixed with absolute ethanol containing 5% hydrogen chloride (30 ml). The red anthocyanin solution was separated by centrifuge. The residue was further decomposed 5 times with 5 portions of 5% ethanolic HCl (20 ml). This gives a better yield of the crude pigments than treatment of the lead salts with all the ethanolic HCl at one time. Anhydrous ether (4 vols) was added to the combined red pigment solution, the mixture kept in a refrigerator overnight, yielding crude pigments (0·996 g) from which bladhianin was isolated.

Isolation of Anthocyanin A. Lead subacetate solution (diluted 5 times) was added in 2 portions (79 ml and 315 ml) to the mother liquor (3·5 l.) from the preparation of the lead salts. The first crop of lead salts, containing mainly Anthocyanin A, was separated before the second portion of the diluted subacetate solution was added. The second crop, containing almost exclusively Anthocyanin A, was decomposed with 0·1% aqueous HCl (700 ml) to give aqueous pigment solution.

The silica powder (40 g) and 0·1% aqueous HCl (35 ml) were transferred to a column. Then, under 30 mm vacuum, the aqueous pigment solution (70 ml) was introduced and eluted with 0·01% ethanolic HCl. After the first narrow band had been removed, 0·02% ethanolic HCl was introduced to elute the main zone. The remainder of the mother liquor of the lead salts was treated in the same way. The eluates were combined (2 l.) and concentrated to 40 ml below 30° under reduced press. Dark red-brown crystals (90 mg) with metallic luster separated and recrystallized from aqueous ethanol HCl to give 60 mg pure Anthocyanin A. (Found: C, 50·47; H, 4·84; Cl, 6·30; OMe, 11·20; H_2O, 3·11. Calc. for $C_{23}H_{23}O_{12}Cl.H_2O$: C, 50·51; H, 5·00; Cl, 6·48; OMe, 11·35; H_2O, 3·29.)

The colour reactions of Anthocyanin A are the same as those given by Scott-Moncrieff for primulin.[8]

Isolation of bladhianin. The crude pigments (3 g) were dissolved successively in 4 portions water (15 ml) and the solutions combined. Fractional precipitation of the picrates by addition of 3 portions of 1% aqueous picric acid (22 ml) kept 20 min at room temp gave successive fractions termed "Picrate I" (585 mg), "Picrate II" (342 mg), "Picrate III" (73 mg) and "Mother liquor A".

Paper chromatography of the pigments obtained by decomposing Picrates I, II and III revealed that the compositions of the picrates, measured by colorimetric method and expressed by approximate ratio of the highest spot:the middle spot:the lowest spot, were Picrate I, 1:0·5:0·05, Picrate II, 1:1:0·5, and Picrate III, 0·1:0·5:1.

Picrate II (684 mg) was ground twice in water (20 ml each) for 10 min. and centrifuged. The combined supernatant liquid was cooled in an ice-salt bath overnight to give precipitate and "Mother liquor B". The compositions checked by paper chromatography and expressed in the approximate ratio of the 3 spots were insoluble picrate (480 mg), 1·00:1·00:0·40: the precipitate (38 mg), 0·00: 0·05:1·00, and Mother liquor B, 0·00:0·001:1·00. Similarly, Picrate III (145 mg) was treated with water to give insoluble picrate (79 mg), precipitate (46 mg) and mother liquor. Each of these 3 parts has the same composition as that of the corresponding part from Picrate II.

Mother liquor A was cooled in an ice-salt bath to give 112 mg of picrates the composition of which was the same as that of Mother liquor B. The picrate was decomposed with 5% absolute ethanolic HCl and reprecipitated with dry ether to give crude anthocyanin chloride (100 mg) which was dissolved in hot water (0·4 ml, 75°) and centrifuged. An equal volume of 2·5% ethanolic HCl was added to the hot aqueous solution. The precipitate (65 mg) was separated after the mixture had been cooled in ice-water and recrystallized 4 times to give crude bladhianin (35 mg). paper chromatography of which showed only the lowest spot. It was further chromatographed on silica powder (100 g). No zone was eluted with aqueous 0·1% HCl or ethanol–water (3:7). When the column was eluted with 0·01% ethanolic HCl, however, 3 zones were seen. The lowest red zone, the middle blue zone, and the highest red zone were eluted successively with 0·01%, 0·02%, and 0·1% ethanolic HCl. After the elution, there was one red zone (4th zone) at the top of the column. The lowest zone was the main fraction, from which bladhianin (10 mg) was obtained.

[13] R. Shindler, *Chem. Zentr.* 779 (1845).

Bladhianin, forms dark violet microcrystals, is easily soluble in water, methanol, and ethanol to form a red solution, sparingly soluble in cold acetone to form a violet solution and insoluble in ether, benzene, and ethyl acetate.

Colour reactions of bladhianin. In aqueous solution: Sodium carbonate, pale green → green-yellow → pale orange; sodium acetate, violet → blue; lead acetate, blue-violet precipitate.

In ethanol solution: Sodium carbonate, blue-violet → dark brown precipitate; sodium acetate, blue; lead acetate, blue-violet precipitate. (Found: C, 45·18; H, 4·82; Cl, 6·26; H_2O 11·68. Calc. for $C_{21}H_{21}O_{12}Cl.3H_2O$: C, 45·45; H, 4·91; Cl, 6·39; H_2O, 11·54%).

Saponification of Anthocyanin A (for any ester linkage).[4] To a red solution of Anthocyanin A (1 mg) in anhydrous 1% ethanolic HCl (2 ml) anhydrous 10% ethanolic KOH (2 ml) was added to give a blue solution. The air above the was replaced by hydrogen and the solution kept at room temp for 1 hr. To this blue solution anhydrous ethanolic HCl was added until the solution turned red. Then 3 volumes of anhydrous ether was added and the precipitate formed was separated by centrifuging and again dissolved in 1% ethanolic HCl to give a red solution. The paper chromatography of this solution developed with 4:1:1 BuOH–AcOH–H_2O at about 20° on a Toyo No. 2 paper showed the same R_f value as that of Anthocyanin A (0·30) indicating no ester linkage is involved in the latter compound.

Hydrolysis of the glycosidic linkage in Anthocyanin A.[4] A solution of Anthocyanin A (5 mg) 20% HCl (1 ml) was boiled for 3 min to give needle crystals of the aglycone which separated while cooling. The filtrate was reserved for the identification of sugar. The aglycone from Anthocyanin A, violet-red needles, gave a positive qualitative tests for malvidin chloride.[5]

The oxidation test. A solution (1 ml) of the aglycone in 5% aqueous HCl was mixed with 10% NaoH (0·5 ml) and shaken for 5 sec. On adding 5 drops of 36% HCl to the above blue solution, the colour turned to reddish, and was extracted with isoamyl alcohol, showing that the aglycone is not decomposed by oxidation.

The R_f values using Toyo No. 2 paper and developed at 28° were 0·39 in 5:1:5 AcOH–36% HCl–H_2O and 0·28 in 5:2:3 80% HCOOH–36% HCl–H_2O. The co-chromatography with an authentic malvidin chloride also showed the same R_f values.

The U.V. spectra of the aglycone was the same as that of authentic malvidin chloride.

Identification of the sugar in the hydrolysate of Anthocyanin A *and in that of bladhianin.* The brown crude sugar solution obtained from the hydrolysis of Anthocyanin A (or bladhianin) was extracted with isoamyl alcohol until both layers became colourless. The aqueous layer was further extracted with benzene 3 times to remove the isoamyl alcohol. The colourless aqueous solution in a watch glass was dried overnight in a evacuated desiccator over sodium hydroxide and calcium chloride, The solid residue was again dissolved in water (0·5 ml) and dried. The unknown sugar in the residue showed on paper chromatography only single spots with several developing solvents, and the R_f values were the same as authentic galatose, which has been used individually and co-chromatographically. The sugar was also identified by conversion to the phenylosazone m.p. 179–181°.

Quantitative hydrolysis of Anthocyanin A. A solution of Anthocyanin A (7·644 mg) in 1·5 ml water was hydrolysed as described above and the reaction product cooled overnight. The crystals of the aglycone separated by centrifuging were washed with 3 drops water. The washings were combined with the mother liquor for the determination of sugar. The aglycone was dried over phosphorous pentoxide at 100–105° under 5 mm vacuum. It weighed 4·925 mg, 64·43% of the anthocyanin. The calculated value for the aglycone in malvidin galactoside monohydrate, $C_{23}H_{23}O_{12}Cl.H_2O$, was 67·06%.

The sugar solution was first diluted with water to 3 ml, then extracted with isoamyl alcohol until the latter became colorless. The isoamyl alcohol extracts were combined and extracted with water (1 ml). The aqueous extract was combined with the sugar solution and again washed with benzene (1 ml) to remove isoamyl alcohol. The benzene washing was extracted with water (1 ml) and the aqueous extract was combined with the sugar solution. The sugar solution was dried in a vacuum desiccator with sodium hydroxide and calcium chloride. The residue was dissolved in water and again evaporated *in vacuo* to dryness. In order to remove HCl which may interfere with the colouration by anthrone, the above procedure (dissolve in water and evaporation) was repeated 5 times. The final residue, a colourless solid mass, was dissolved in water (8 ml). The solution (pH 6·12) gave no precipitate with silver nitrate solution. The amount of galactose in this solution was determined as

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PHOTOCHEMICAL TRANSFORMATIONS—VI[1,2]

ISOMERIZATION OF CYCLOHEPTADIENE AND CYCLOHEPTATRIENE

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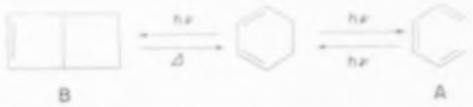
Abstract—Irradiation of 1,3-cycloheptadiene in ether solution gave Δ^5-bicyclo [3.2.0] heptene, the structure of which was established by degradation to *cis*-cyclopentane-1,2-dicarboxylic acid and by dihydrogenation to the known bicyclo [3.2.0] heptane. Irradiation of 1,3,5-cycloheptatriene in ether gave the known $\Delta^{2,5}$-bicyclo [3.2.0] heptadiene. Both photoproducts upon pyrolysis were reconverted to their respective seven membered ring progenitors.

WHEN a conjugated homoannular diene is irradiated in solution with ultraviolet light, it is transformed into valence tautomeric structures, i.e. only carbon–carbon bonds and not carbon–hydrogen bonds are involved in the reaction. Depending on the structure of the starting diene either ring cleavage (product A)[4–7] or intramolecular cyclization[8]



(bridging, product B) occurs. In some cases the ring cleavage reaction has been found to be a reversible photochemical reaction[4,5] but such cannot be the case in the bridging reaction since the product formed no longer possesses a chromophoric group capable of being excited (in a preparative sense) by available light sources. Such bridged structures, however, being highly strained can be reconverted to the starting diene by the action of heat. In the six membered ring system both with the dienes[4–7] and the dienones[9] the preferred reaction is the cleavage reaction and, to date, only two cases of a bridging reaction in this series (photoisopyrocalciferol and photopyrocalciferol[8]) have been reported.

In order to evaluate the generality of the intramolecular ring closure reaction, it is desirable to study a system in which the ring cleavage reaction is prohibited. The 1,3-cycloheptadiene ring system is such a structure and, indeed, recently it has been shown that 2,6,6-trimethyl-2,4-cycloheptadiene-1-one (eucarvone) is readlily transformed, photochemically, to its valence tautomeric bicylco[3.2.0]-heptene system.[10]

Irradiation of 1,3-cycloheptadiene (I) in ether solution with a G.E. AH-6 mercury

[1] For paper V, see W. G. Dauben and J. A. Ross, *J. Amer. Chem. Soc.* **81**, 6521 (1959).
[2] This work supported in part by Grant No. A–709 (C–6)-Bio., U.S. Public Health Service.
[3] Postdoctoral Fellow, U.S. Public Health Service, 1960–1961.
[4] L. Velluz, G. Amiard and B. Goffinet, *Bull. Soc. Chim. Fr*, 882 (1957).
[5] M. P. Rappoldt and E. Havinga, *Rec. Trav. Chim.* **79**, 369 (1960) and earlier papers.
[6] R. L. Autrey, D. H. R. Barton and W. H. Rausch, *Proc. Chem. Soc.* 55 (1959).
[7] M. P. Rappoldt, *Rec. Trav. Chim.* **79**, 392 (1960).
[8] W. G. Dauben and G. J. Fonken, *J. Amer. Chem. Soc.* **81**, 4060 (1959).
[9] For an excellent summary of such reactions, see D. H. R. Barton, *Helv. Chim. Acta* **42**, 2604 (1959).
[10] G. Büchi and E. M. Burgess, *J. Amer. Chem. Soc.* **82**, 4333 (1960).

2·375 mg. (31·07% of the anthocyanin) by the anthrone method using authentic galactose solution as control.[14] The calculated value for monogalactoside was 32·94%.

Determination of the position of the sugar.[6] An equal volume of aqueous 0·25% ferric chloride was was mixed with 0·004% pigment solution (in aqueous 1% HCl solution). The resulting red colour did not change during a period of 3 days. This shows that the position 3 is not free. The same experiment was carried out with the aglycone from Anthocyanin A for control. The solution became colourless within 3 min, showing that the 3-position is free.

Saponification of bladhianin (for any ester linkage). The similar treatment of bladhianin as that of Anthocyanin A gave unreacted material as shown from the following R_f values when co-chromatographed with bladhianin (Toyo No. 2 paper): 4:1:1 BuOH–AcOH–H_2O, 0·16; 5:1:4 80% HCOOH–36% HCl–H_2O, 0·41.

Hydrolysis of the glycosidic linkage in bladhianin. A solution of bladhianin (5 mg) in 20% HCl (1 ml) was boiled for 3 hr and extracted with isoamyl alcohol. The aglycone obtained was soluble in water. It gave the Robinson's colour reactions for delphinidin.

In contrast to the aglycone of Anthocyanin A, that of bladhianin was decomposed in the oxidation test by alkalinizing its solution followed by shaking for 5 sec.

The aglycone showed the same R_f values as those of authentic delphinidin isolated from the hydrolysate of the pigment in the skins of the fruits of *Solanum melongena*[15] on co-chromatography on Toyo No. 2 paper at about 28° as follows: 5:1:5 AcOH–36% HCl–H_2O, 0·20; 5:2:3 80% HCOOH–36% HCl–H_2O, 0·14.

The U.V. spectra of the aglycone from bladhianin was the same as that of delphinidin.

The sugar from bladhianin as that in Anthocyanin A is galactose.

The quantitative hydrolysis of bladhianin (9·463 mg) with 20% HCl gave sugar (2·896 mg, 30·60% of bladhianin). The calculated figure for delphinidin monogalactoside trihydrate, $C_{21}H_{21}O_{12}Cl.3H_2O$, is 32·47% sugar. The amount of dried delphinidin chloride obtained from the isoamyl alcohol extract of the hydrolysate was 5·480 mg, 57·91% of bladhianin (Calc. for anhydrous aglycone, 59·84%).

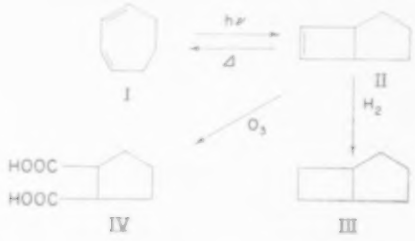
The position of the sugar substituent was determined by the oxidation test with ferric chloride. On adding ferric chloride solution, the red solution of bladhianin decolourized within 30 min, proving the 3-position free. The red colour of a solution of the aglycone from bladhianin decolourized after 3 min. With the ferric chloride test, decolourization is complete in 35 min if position 3 is free. On the other hand, the colour is unchanged for 3 days if 3-position is not free.[6]

Exhaustive methylation and hydrolysis of bladhianin. Bladhianin (2 mg) was dissolved in 3 drops of 1 N NaOH. The colour of the solution changed instantly from red to blue. With vigorous stirring, 0·5 ml freshly distilled dimethyl sulphate and 30% aqueous NaOH (2 ml) was added dropwise during 1·5 hr in nitrogen atm and stirring was continued for another hour. The orange-yellow mixture was neutralized with 2 N HCl and made about 4 N with 36% HCl. After heating at 100° for 30 min the colour (orange-yellow) of the mixture remain unchanged, proving the 5-position to be free.

Acknowledgments—The authors wish to thank Prof. K. Hayashi (Tokyo University of Education) for advice and samples of malvidin, malvidin 3-galactoside (synthetic), and other pigments for identification and to Dr. T. Imai (Sankyo Co., Tokyo) for elementary analyses.

[14] J. R. Helbert and K. D. Brown, *Analyt. Chem.* **27**, 1791 (1955); D. D. Morris, *Science* **107**, 254 (1948).
[15] C. Kuroda and M. Wada, *Proc. Imp. Acad* **9**, 51 (1933).

lamp for 40 hours gave a photoisomer (II) in 42 per cent yield. The photoisomer possessed bands in the infrared at 3020, 1560 and 735 cm^{-1}, characteristic of a cyclobutene.[11,12] The ultraviolet spectrum showed only weak end absorption (ε_{205} 940). The nuclear magnetic resonance spectrum possessed three general bands whose integrated intensities were in the ratio of 2:2:6. These spectral features were indicative of valence tautomeric structure II, Δ^6-bicyclo[3.2.0]heptane, for the photoproduct. In the NMR, the low field singlet at 4·20 τ was assigned to the cyclobutene protons, the singlet structure suggesting identity of the vinyl protons. The small coupling with the adjacent ring juncture hydrogens could not be resolved. A doublet centered at 6·89 τ was assigned to the allylic ring juncture protons, the doublet suggesting identity of the protons and their coupling with an adjacent methylene group. Finally, a large broad band centered at 8·58 τ was assigned to the six protons of the remaining saturated methylene groups.



The bicyclic nature of the ring system was established by dihydrogenation of II to the known bicyclo[3.2.0]heptane (III).[13] The presence of the cyclobutene ring was shown by the isolation of *cis*-cyclopentane-1,2-dicarboxylic acid (IV) from the ozonization of the II. Finally, when the photoisomer was pyrolyzed at 400° it was converted back to cycloheptadiene, a thermal rearrangement expected of the valence tautomeric structure II.

The finding of the facile conversion of 1,3-cycloheptadiene to its bicyclic valence tautomer prompted the investigation of the photochemical reaction of 1,3,5-cycloheptatriene (V). It is well established[14,15] that the related tropolones undergo the bridging reaction but the spectral character of this type of compound makes it quite different from the unsubstituted triene. With 1,3,5-cycloheptatriene there are two valence tautomeric structures which can be formed by bridging, one the norcaradiene (VI) and the other the $\Delta^{2,6}$-bicyclo[3.2.0]heptadiene (VII). Previous workers[16]

[11] R. C. Lord and M. V. Evans, Jr., *J. Amer. Chem. Soc.* **79**, 2401 (1957).
[12] There were also bands of lesser intensity at 1625 and 1670 cm^{-1} which have been assigned as overtones of methylene vibrations.
[13] A. T. Blomquist and J. Kwiatek, *J. Amer. Chem. Soc.* **73**, 2098 (1951); E. Vogel, private communication.
[14] E. J. Forbes, *J. Chem. Soc.* 3864 (1955); P. D. Gardner, R. L. Brandon and G. R. Haynes, *J. Amer. Chem. Soc.* **79**, 6334 (1957).
[15] O. L. Chapman and D. J. Pasto, *J. Amer. Chem. Soc.* **82**, 3642 (1960).
[16] W. E. Doering and L. H. Knox, *J. Amer. Chem. Soc.* **75**, 247 (1953).

attempted to prepare the norcaradiene by the reaction of diazomethane with benzene but the finding of only 1,3,5-cycloheptatriene led to the conclusion that at ordinary temperatures the norcaradiene is rapidly isomerized to the triene. Such a thermal instability of the diene would prohibit its buildup in a photochemical reaction run at room temperature. On the other hand, the $\Delta^{2,6}$-bicyclo[3.2.0]heptadiene (VII) has been prepared from cyclopentadiene[17] and has been shown to be thermally stable to temperatures up to 200°. Since such a valence tautomer would be stable to ultraviolet light, the photochemically induced bridging reaction could be expected to yield such a material.

Irradiation of 1,3,5-cycloheptatriene (containing a small amount of toluene) in ether solution under the above conditions for a period of 200 hours gave an isomeric photoproduct in 34 per cent yield. In agreement with the expected structure, VII, the photoproduct possessed physical properties which were identical with those reported for VII.[16] The ultraviolet spectrum showed no maximum (ε_{205} 2340) and the infrared spectrum in addition to bands at 3050, 1605 and 1560 cm^{-1}, the last two being characteristic of a cyclopentene and cyclobutene, showed the characteristic three overtone bands at 1625, 1660 and 1690 cm^{-1}.[18] The nuclear resonance spectrum showed three major band series whose integrated areas were in the ratio of 4:2:2. The bands for the two vinyl protons of the cyclobutene ring were centered at 3·67 and 3·92 τ and each band was a doublet with a 3 cps splitting; as in II the coupling with the ring juncture protons was not detected. The cyclopentene proton absorption was centered at 4·36 τ and appeared as a multiplet. The second series of bands were at 6·38 and 6·73 τ, each band representing one proton, and these bands were assigned to the ring juncture protons. The sole methylene group absorbed at 7·67 τ. In addition to these spectral properties which clearly define the structure of the photo-product, the material upon tetrahydrogenation yielded bicyclo[3.2.0]heptane (III) and upon pyrolysis at 400° reconverted to the starting triene.

This ultraviolet light-induced conversion of cycloheptadiene and cycloheptatriene to the bridged valence tautomeric structures as well as the previously reported[8,10,14,15] results with the pyrocalciferols, tropolones and eucarvone clearly indicate the general occurrence of photochemical intramolecular cyclization or bridging reactions.

EXPERIMENTAL[19]

Δ^6-Bicyclo[3.2.0]heptene (II). A solution (21·8 g; 0·23 mole) 1,3-cycloheptadiene[20] [b.p. 120–122°, λ_{max}^{EtOH} 246 mμ (ε 7750)] in 2 l. of dry ether was irradiated with a G.E. AH-6 high pressure mercury arc lamp (internal probe). The solution was agitated by a slow stream of nitrogen and the course of the irradiation followed by ultraviolet spectroscopy. After a period of 40 hr (this time varies with the age of the lamp) the characteristic ultraviolet absorption of the diene was absent. The ether was removed by distillation through a 1 meter tantalum spiral column and product distilled through the same column, b.p. 96–98°, n_D^{25} 1·4536, ε_{205}^{EtOH} 940, yield 6·43 g (29·5%). The residual yellow viscous oil was distilled through a short path molecular still and from the distillate an additional 2·9 g (13·3%) of photoproduct was obtained. The Δ^6-bicyclo[3.2.0]heptene was homogeneous to GLC over a 10-ft. asphalt column at 100°; the starting diene is readily separated under these conditions.
(Found: C, 89·39; H, 10·83; Calc. for C_7H_{10} (94·15): C, 89·29; H, 10·71%).

[17] E. Vogel, *Angew. Chem.* **68**, 189 (1956); M. V. Evans and R. C. Lord, *J. Amer. Chem. Soc.* **82**, 1876 (1960).
[18] The authors are indebted to Professor M. V. Evans, Jr., for kindly supplying the characteristic I.R. bands of VII.
[19] All analyses were performed by the Microanalytical Laboratory, College of Chemistry, University of California.
[20] E. Pesch and S. L. Friess, *J. Amer. Chem. Soc.* **72**, 5756 (1950).

Bicyclo[3.2.0]*heptane* (III). A solution (1·07 g; 11·4 mmoles) Δ^6-bicyclo[3.2.0]heptene in 45 ml 95% ethanol was hydrogenated over 63 mg prereduced platinum oxide at atm press and 25°. After 70 min, 275 ml (11·4 mmoles) hydrogen had been absorbed and no further uptake was observed. The catalyst was filtered and the ethanolic filtrate partitioned between water and ether. The ethereal layer was washed with water, dried and then swirled with 16 g alumina (Woelm, Act. III). The ether was removed by careful distillation through a 1-meter tantalum spiral column and the residue distilled through a short-path molecular still, yield 715 mg (67%). The distillate upon GLC over a 10-ft. asphalt column at 100° showed less than 1% starting material. An analytical sample of bicyclo-[3.2.0]heptane was collected from GLC under the above conditions, n_D^{20} 1·4525 (lit.[12] n_D^{20} 1·4532).

(Found: C, 87·19; H, 12·71; Calc. for C_7H_{12} (96·17): C, 87·42; H, 12·58%).

Ozonolysis of Δ^6-*bicyclo*[3.2.0]*heptene* (II). Ozone was passed through a solution (500 mg. 5·3 mmoles) II in 100 ml methylene chloride cooled in a Dry Ice-isopropanol bath at the rate of 0·41 mmole/min for 21 min. The resulting solution had the characteristic blue color of a methylene chloride solution of ozone. The solvent was removed under reduced press and the residual oily ozonide was allowed to react with 30% hydrogen peroxide in alkaline solution on a steam-bath for 2 hr. The solution was acidified and evaporated to dryness. The residue was digested with chloroform, the chloroform solution decolorized and the solvent evaporated. The remaining oil was crystallized from ether–petroleum ether (30–60°), yield 91 mg (11%), and after two additional recrystallizations from the same solvents gave pure *cis*-cyclopentane-1,2-dicarboxylic acid (IV), m.p. 137–139°. A mixed m.p. with an authentic sample, prepared from the *trans*-diacid,[21] is 137–139°, and the infrared spectra (KBr pellet) of the two samples of diacid were identical.

Pyrolysis of Δ^6-*bicyclo*[3.2.0]*heptene* (II). The pyrolysis apparatus consisted of a 7-mm (I.D.) Pyrex tube packed to a height of 16 cm with Pyrex helices and heated to 400–420°. A slow stream of nitrogen was constantly passed through the apparatus and the material to be pyrolyzed was slowly injected into the column from a syringe. The bicycloheptene, II (250 mg, 2·6 mmoles), was injected and the pyrolysate collected in a trap cooled in a Dry Ice–isopropanol bath, yield 157 mg (63%). The pyrolysate was homogeneous to GLC over a 10 ft. asphalt column at 100° and had an infrared spectrum which was superimposable on that of 1,3-cycloheptadiene.

$\Delta^{2,6}$-*Bicyclo*[3.2.0]*heptadiene* (VII). A solution (26·0 g; 0·28 mole) freshly distilled 1,3,5-cyclo-heptatriene[22,23] in 2 l. dry ether was irradiated as above for 200 hr at which time more than 90% of the triene spectrum had disappeared. The ether was removed through a 1-meter tantalum spiral column and the product distilled through the same column, yield 8·80 g (34%), b.p. 97–98° (lit[17,24] b.p. 96·0–97·5°), ϵ_{205}^{EtOH} 2340. By GLC on a DEGS column at 40°, the distillate was found to contain 95–97% of $\Delta^{2,6}$-bicyclo[3.2.0]heptadiene and 3–5% of toluene and unchanged starting material. A non-volatile residue of 11·5 g was recovered and presumably is polymeric material.

The photoproduct was purified by GLC using a ½ inch diameter DEGS column at 40° and the material collected was dried over lithium aluminum hydride, n_D^{23} 1·4721 (lit[24] n_D^{20} 1·4751.

(Found: C, 91·25; H, 8·94; Calc. for C_7H_8 (92·13): C, 91·25; H, 8·75%).

Hydrogenation of $\Delta^{2,6}$-*bicyclo*[3.2.0]*heptadiene* (VII). A solution (603 mg; 6·6 mmoles) bicyclo-heptadiene (VII) in 15 ml 95% ethanol was hydrogenated over 38 mg prereduced platinum oxide at atm press and 25°. After 100 min 328 ml (13·5 mmoles) hydrogen had been absorbed. The product was processed as before and collected from GLC (DEGS ½ inch column at 40°) and the infrared spectrum of the material was superimposable on that of bicyclo[3.2.0]heptane. Co-injection of hydrogenated materials from the bicycloheptene and bicycloheptadiene on a DEGS column gave a single band.

Pyrolysis of $\Delta^{2,6}$-*bicyclo*[3.2.0]*heptadiene* (VII). The bicycloheptadiene VII (86 mg; 0·91 mmole) was pyrolyzed as described above. The product (32 mg, 37%) was homogeneous to GLC on a DEGS column at 40° and its infrared spectrum (CS_2) was identical with that of 1,3,5-cycloheptatriene (collected from GLC and free of toluene).

[21] L. N. Owen and A. G. Peto, *J. Chem. Soc.* 2383 (1955).
[22] Kindly supplied by the Shell Development Corporation, Emeryville, California.
[23] The 1,3,5-cycloheptatriene was distilled through a Vigreux column, b.p. 114–116° (lit b.p. 117°, W. G. Woods, *J. Org. Chem.* **23**, 110 (1958)), and the distillate contained a few per cent of toluene.
[24] E. Vogel, private communication.

Tetrahedron, 1961, Vol. 12, pp. 190 to 191. Pergamon Press, Inc. Printed in Northern Ireland

BOOK REVIEWS

R. M. ACHESON: **An Introduction to the Chemistry of Heterocyclic Compounds.** Interscience Publishers, New York, London, 1959. 342 pp., $5.00, 35s.

THE object of this work, as stated in the Preface, is to provide an account of the modern aspect of heterocyclic chemistry suitable for the use of advanced students.

The dearth of such text-books is not so serious now as it was when Dr. Acheson embarked on his project, because meanwhile the encyclopaedic accounts in the Elderfield series have been supplemented by shorter books, for example those by Albert, Bentley, and Katritzky and Lagowski. It is interesting to see how the slightly differing points of view of these authors are reflected in their treatment of similar material. Acheson's modification is essentially descriptive, a kind of Sidgwick's *Organic Chemistry of Nitrogen* (revised by Baker and Taylor) brought selectively up to date.

The purpose, which has been largely achieved in a satisfactory manner, has evidently been to display the chemical character of the substances treated as completely as possible. We are told what happens and special characteristics are pin-pointed, so that the reader of this book traverses the region like a sightseer in an observation car. He will find much to awaken his curiosity and will be stimulated to think for himself. Unfortunately the theoretical background of heterocyclic chemistry is not sufficiently clearly expounded. The old-fashioned use of the concept of canonical forms is adopted throughout and there are few illustrations of the value of representation of electronic displacements in conjugated systems, which are so very relevant to explanations of chemical properties in the series.

Again the maps of π-electron densities of typical compounds, derived theoretically, are reproduced without any clear indication as to how they may be used. For example, that for quinoline is stated (p.217) to suggest that electrophilic reagents will attack the carbocyclic ring at positions 5- and 8-. But the values given are:

3-, 0·978; 5-, 0·956; 6-, 0·989; 7-, 0·947; 8-, 1·003.

It must be emphasized that such figures have never been related in a satisfactory manner to orientation phenomena. The figures showing angles of bonds and distances between atoms are more valuable, being experimentally founded for one thing, but perhaps they will be more appreciated by the research worker than by the student.

The omission of the alkaloids is understandable but unfortunate in that much fundamental chemistry necessarily went with them.

There is a little too much of the three and four rings and space saved at the beginning could have been well used at the end, that is, on more extended description of the pyrimidines and similar groups.

In spite of these minor criticisms, the book will be an important addition to the library of the student of organic chemistry. It is an original work and a kind of hybrid between a textbook and a reference book. This stimulating volume can be warmly recommended to advanced students of organic chemistry and of biochemistry and especially to those who are already well versed in the underlying theoretical basis of the science. They will here find ample material to which they may apply the principles of the electronic theories of structure and reactions.

R. ROBINSON

P. B. D. DE LA MARE and J. H. RIDD: **Aromatic Substitution: Nitration and Halogenation.** Butterworths Scientific Publications, London, Academic Press, New York, 1959. 252 pp., 50s.

THIS monograph is a new and original work in that the material has not been previously collected in one place. The emphasis is on reaction mechanism which is adequately discussed in terms of kinetic and other physico-chemical principles, the nature of the reactants, and the conditions of the experiments.

Sections on the ground states of molecules, transition states and equilibria in solutions are followed by consideration of the methods used for the identification of reaction paths and the possible stages of interaction. This includes the evidence for complex formation and the molecular species, on the nitric acid and derivative side, which are directly concerned in the nitration process. Here the inclusion of practical details gives a welcome air of verisimilitude to the narrative. Consideration is also given to nitrosation and nitration by way of the lower stage of oxidation.

The treatment of orientation in aromatic nitration is also interesting but far from satisfactory due to the capricious selection of the studies to which reference is made. Moreover the references made are not infrequently to later workers, earlier investigations of the same topics being completely ignored. The statement in the Preface "It is hoped that the literature citations are reasonably representative, but they have been chosen to illustrate scientific points and not to adjudicate on matters of priority" discloses some anticipation of criticism. It is not as disarming as it appears intended to be and does not justify the failure to mention the true origins of ideas or discoveries.

This work gives a thoroughly biased account of the historical side of the qualitative electronic theory which is in any case not presented as carefully, or even lucidly, as the excellent treatments of reaction mechanism. The chapters dealing with halogenation, rearrangements, polycyclic substances and heterocyclic aromatics are similarly highly interesting but with the same defects. The wave mechanical treatment of valency and similar approaches are not used to a large extent in the body of the work but are separately, and on the whole acceptably, discussed in a later chapter.

The book is a thoughtful contribution to our understanding of one of the best explored fields of organic chemical reactions, but there are serious omissions and selective dogmatism creeps into the discussion in several places.

R. Robinson

VOL. 12 1961

Tetrahedron, 1961, Vol. 12, p. 192. Pergamon Press, Inc. Printed in Northern Ireland

A list of some of the papers to be published in future issues

N. PETRAGNANI: Aryl tellurium trihalides—II. Condensation reaction with methylketones and aromatic compounds containing electron-repelling groups.

KATSUMI KOTERA: The stereochemistry of lycorane—II. (−)β-Lycorane.

KATSUMI KOTERA: The stereochemistry of lycorane—III. γ- and β-Lycorane.

W. NAGATA: Totalsynthetische Untersuchungen an Steroiden. Parts VII, VIII & IX.

W. NAGATA, T. TERASAWA, S. HIRAI und KEN'ICHI TAKEDA: Totalsynthetische Untersuchungen an Steroiden—X.

T. KAMIKAWA and T. KUBOTA: Natural furan derivatives—VII. The presence of a seven-membered α,β-unsaturated lactone in obacunone.

T. MATSUURA, T. KAMIKAWA and T. KUBOTA: Natural furan derivatives—VIII. Relationship between the furan ring and six- and seven-membered lactone rings in obacunone.

S. K. BALASUBRAMANIAN: Studies in stereochemistry—I. Stereospecific routes to *trans-*, *anti-* and *cis-syn*-Δ^8-dodecahydrophenanthrenes.

C. A. COULSON: Bond lengths in the cyclo-octatetrene dianion $C_8H_8^{--}$

K. HEYNS, H. PAULSEN und H. SCHROEDER: Die Umsetzung von Ketohexosen mit sekundären Aminosäuren und sekundären Aminen.

A. T. BALABAN, P. T. FRANGOPOL, M. MĂRCULESCU and J. BALLY: Factors affecting stability and equilibria of free radicals. Steric factors in hydrazyls.

J. B. LEE and M. M. EL SAWI: Sugar esters—I. Oxide formation in the synthesis and hydrolysis of some fluorides and phosphate esters.

KEN'ICHI TAKEDA, HITOSHI MINATO and SATOKO NOSAKA: Studies on sesquiterpenoids—III. Some derivatives of guaiol.

A. SOMASEKAR RAO, A. PAUL SADGOPAL and S. D. BHATTACHARYYA: Terpenoids—XXV. Structure of saussurea lactone.

GEORGE SOSNOVSKY: Reactions of t-butyl peresters—III. Cuprous bromide-catalyzed reaction of peresters with ethers.

R. BOGNÁR and P. NÁNÁSI: New types of the *trans*-glycosylation reaction.

K. ALDER und M. FREMERY: Zur Darstellung *o*-Chinoider Kohlenwasserstoffe und deren verhalten Gegenüber Philodienen.

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BOND LENGTHS IN THE CYCLO-OCTATETRAENE DIANION $C_8H_8^{--}$

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(*Received* 14 *November* 1960)

Abstract—Simple molecular orbital calculations suggest that the $C_8H_8^{--}$ dianion is planar with equal bond lengths 1·409 Å.

IT has recently been shown by Katz and Strauss[1] using nuclear magnetic resonance and electron-spin resonance that the cylco-octatetraene dianion $C_8H_8^{--}$ must be highly stabilized by resonance, and probably be flat. Now it can be shown that the ground state of a hypothetical flat neutral C_8H_8 would have unequal bond lengths, in distinction to the case of benzene C_6H_6 where resonance causes all the bonds to be equal (the "$4n + 2$ rule"). It is important, therefore, to enquire whether the dianion is or is not a regular octagon.

FIG. 1.

To do this consider a plane molecule (Fig. 1) with alternating lengths r_1, r_2 and corresponding molecular-orbital integrals β_1, β_2. If we suppose that $r_1 < r_2$, then $|\beta_1| > |\beta_2|$, and perfectly straightforward m.o. calculations with neglect of all overlap integrals show that the energies of the 8 allowed orbitals for the π-electrons are given by

$$\varepsilon_1 = (\beta_1 + \beta_2) = -\varepsilon_8$$

$$\varepsilon_2 = \varepsilon_3 = \sqrt{(\beta_1^2 + \beta_2^2)} = -\varepsilon_6 = -\varepsilon_7$$

$$\varepsilon_4 = (\beta_1 - \beta_2) = -\varepsilon_5$$

Fig. 2 shows the appearance of these energies, both for the case of $r_1 = r_2$ and $r_1 < r_2$. The most notable difference when the octagon is not regular, lies in the splitting of the previous degenerate zero-energy level. In the case of neutral cyclo-octatetraene with 8 π-electrons it can be seen that the previous degeneracy is removed (by the operation of a pseudo Jahn–Teller effect similar to that already known in cyclo-butadiene C_4H_4)[2] so that the molecule becomes distinctly more stable. In the case of the dianion, with 10 π-electrons, the lowest five orbitals are doubly occupied, and it is not immediately obvious whether or not the stability is increased as a result of the distortion. We can show, however, that although it turns out that the π-electrons favour a distorted

[1] T. J. Katz, *J. Amer. Chem. Soc.* **82**, 3784 (1960); T. J. Katz and H. L. Strauss, *J. Chem. Phys.* **32**, 1873 (1960).
[2] C. A. Coulson, *J. Chem. Soc.* Special Publication No. 12, 85 (1958).

octagon, the influence of the underlying σ-bonds is sufficiently strong in favour of equal bonds as to cause the molecule to assume a regular octagonal shape.

First let us show that the π-electron energy E_π favours a distorted octagon. E_π takes the form

$$E_\pi = 2\varepsilon_1 + 4\varepsilon_2 + 2\varepsilon_3 + 2\varepsilon_4$$
$$= 2(\beta_1 + \beta_2) + 4\sqrt{(\beta_1^2 + \beta_2^2)}.$$

We shall suppose that β varies with r according to the exponential law used by Longuet-Higgins and Salem[3], viz. $\beta = \beta_0 e^{-a(r-r_0)}$. Then if we start with all links equal to r_0,

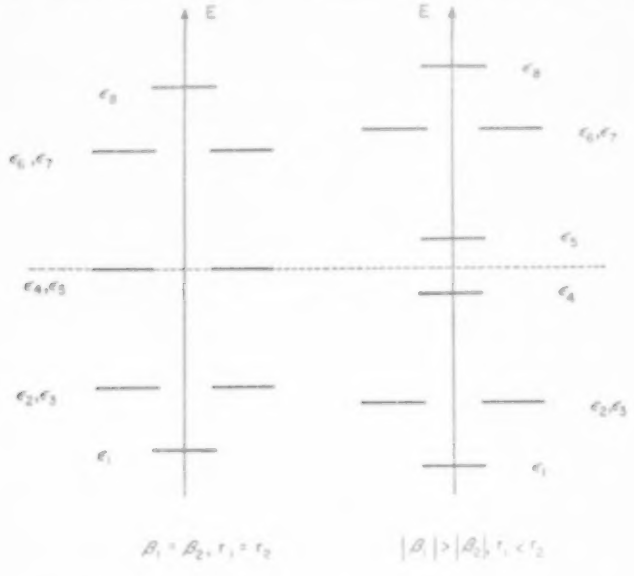

FIG. 2.

with equal resonance integrals β_0, we may consider the particular distorted shape of Fig. 1 for which $r_1 = r_0 - x$, $r_2 = r_0 + x$, so that

$$\beta_1 = \beta_0 e^{ax}, \qquad \beta_2 = \beta_0 e^{-ax}.$$

Then
$$\varepsilon_1 = 2\beta_0 \cosh ax \qquad = 2\beta_0(1 + \tfrac{1}{2}a^2x^2 + \ldots)$$
$$\varepsilon_2 = 2^{1/2}\beta_0 \sqrt{(\cosh ax)} = 2^{1/2}\beta_0(1 + \tfrac{1}{4}a^2x^2 + \ldots)$$
$$\varepsilon_3 = 2\beta_0 \sinh ax \qquad = 2\beta_0(ax + \tfrac{1}{6}a^3x^3 + \ldots).$$

Thus as x increases from zero E_π is lowered by an amount roughly equal to Kx^2, where $K = (2 + \sqrt{2})\, a^2 |\beta_0|$. This shows that E_π favours alternating bond lengths.

To determine the actual equilibrium configuration when the σ-bond energy E_σ is included, we write

$$E = E_\pi + E_\sigma$$

where
$$E_\sigma = 4[\tfrac{1}{2}k(r_1 - s)^2 + \tfrac{1}{2}k(r_2 - s)^2].$$

[3] H. C. Longuet-Higgins and L. Salem, *Proc. Roy. Soc.* A **251**, 172 (1959).

In this expression s is the length of a pure single carbon–carbon trigonal bond, and k is its force constant.

It is obvious that the energy E is stationary at $r_1 = r_2$. If we can show that it is a minimum at this point, then we have shown that the regular structure is preferred. By direct differentiation, using the fact that $d\beta/dr = -a\beta$;

$$\frac{\partial^2 E}{\partial r_1^2} = 4k + 2a^2\beta_1 + \frac{4a^2\,\beta_1^2(\beta_1^2 + 2\beta_2^2)}{(\beta_1^2 + \beta_2^2)^{3/2}}$$

and a similar equation for $\partial^2 E/\partial r_2^2$. Also

$$\frac{\partial^2 E}{\partial r_1 \partial r_2} = -\frac{4a^2\,\beta_1^2\,\beta_2^2}{(\beta_1^2 + \beta_2^2)^{3/2}}$$

If we put $s = 1{\cdot}50$ Å, and accept the value $a = 2{\cdot}683$ Å^{-1}, as used by Coulson and Golebiewski[4], and put $k = 4{\cdot}8\ 10^5$ dynes/cm, it is easily verified that the first term in the expression for $\partial^2 E/\partial r_1^2$ (which is due to the σ-bonds) is positive and about three times as large as the other two terms (which are negative and due to the π-bonds). Also $(\partial^2 E/\partial r_1^2)(\partial^2 E/\partial r_2^2) > (\partial^2 E/\partial r_1 \partial r_2)^2$. Thus the regular octagon is stable and this stability is independent of small changes that we might wish to made in the numerical values of s, a and k. The actual length in the equilibrium state comes out to be $1{\cdot}409 \pm 0{\cdot}001$ Å. This is notably longer than in benzene (1·397 Å) in agreement with the fact that although the anion does possess considerable resonance stability, its π bond order 0·604 is smaller than that of benzene 0·667. This difference accounts for the 0·012 Å increase in length. It may be worth adding that all reasonable order-length curves give approximately the same value for this increase.

[4] C. A. Coulson and A. Golebiewski, unpublished.

Tetrahedron, 1961, Vol. 12, pp. 196 to 204. Pergamon Press, Inc. Printed in Northern Ireland

STUDIES IN STEREOCHEMISTRY—I

STEREOSPECIFIC ROUTES TO *TRANS- ANTI-* AND *CIS- SYN-*Δ^{8}-DODECAHYDROPHENANTHRENES

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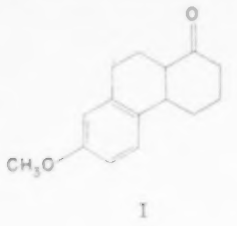
(*Received* 15 *August* 1960)

Abstract—Reduction of *trans*-1-oxo-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene (XI) by lithium tri-t-butoxyaluminohydride gave *trans*-1β-hydroxy-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene (XII) which on lithium–liquid ammonia reduction gave *trans-anti*-1β-hydroxy-7-oxo-$\Delta^{8(14)}$-dodecahydrophenanthrene (XIII). Reduction of *cis*-1-oxo-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene (XV) by sodium borohydride gave *cis*-1α-hydroxy-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene (XVI) which on lithium–liquid ammonia reduction gave *cis-syn*-1α-hydroxy-7-oxo-$\Delta^{8(14)}$-dodecahydrophenanthrene (XVII).

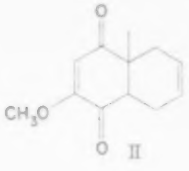
THE method of conformational analysis[1] has been employed with considerable success to the problem of the differences in the thermodynamic stabilities of stereoisomers in polycyclic systems. Thus the greater stability of *trans*- over *cis*-decalin is well-rationalized,[2] as also the stability orders in the perhydrophenanthrene and hydrindane series.[3,4] The introduction of functional groups like the ketogroup into the saturated systems, however, modifies the relative stabilities of the stereoisomers.[5] The conformational alterations introduced by double bonds are less easily understood and have recently been the subject of interesting speculation.[6–9] Some of the experimentally observed deviations in stability order are given below. The *cis*- and *trans*-forms of the octahydrophenanthrone (I), which is conformationally equivalent to an octalone, are present in the ratio of 1:4 in the equilibrium mixture,[10] in contrast to the case of the decalones, where the equilibrium is entirely in favour of the *trans*-isomer. A more complicated example is the diketone (II), the *cis*- and *trans*-forms of which are of the same order of stability.[11] The metal–alcohol reduction of the central double bond of the tetrahydrochrysene derivative (III) yields nearly equal amounts of the *cis*- and *trans*-forms of the corresponding hexahydrochrysene.[12,13] Since carbanion reductions proceed with predominant thermodynamic control,[14] this could be taken as evidence that the two stereoisomers are of equal stability. Recently Wenkert and

[1] D. H. R. Barton and R. C. Cookson, *Quart. Rev.* **10**, 44 (1956).
[2] R. B. Turner, *J. Amer. Chem. Soc.* **74**, 2118 (1952).
[3] W. S. Johnson, *Experientia* **7**, 315 (1951); *J. Amer. Chem. Soc.* **75**, 1498 (1953).
[4] G. Quinkert, *Experientia* **13**, 381 (1957).
[5] P. A. Robins and J. Walker, *J. Chem. Soc.* 3960 (1954); 1789 (1955); *Chem. & Ind.* 772 (1955); W. Klyne, *Experientia* **12**, 119 (1956).
[6] E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.* **77**, 2505 (1955).
[7] R. B. Turner, W. R. Meador and R. E. Winkler, *J. Amer. Chem. Soc.* **79**, 4122 (1957).
[8] D. A. H. Taylor, *Chem. & Ind.* 250 (1954).
[9] A. S. Dreiding, *Chem. & Ind.* 1419 (1954).
[10] A. J. Birch, H. Smith and R. E. Thornton, *J. Chem. Soc.* 1339 (1957). We are greatly indebted to Prof. A. J. Birch, F.R.S., for encouraging us to undertake the present study.
[11] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *J. Amer. Chem. Soc.* **74**, 4223 (1952).
[12] A. J. Birch and H. Smith, *J. Chem. Soc.* 4909 (1956).
[13] P. A. Robins and J. Walker, *J. Chem. Soc.* 4984 (1957).
[14] D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.* 3045 (1954).

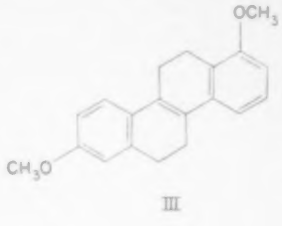
Jackson have made the interesting observation that the ketoesters (IV, V and VI) are highly enolic, whereas the ester (VII) is enolized only to a minor extent.[15] This may be, in part at least, due to the subtle conformational effect of the type noted above.



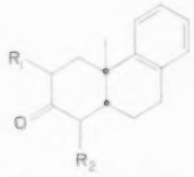
I



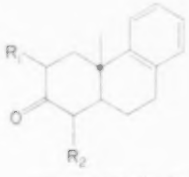
II



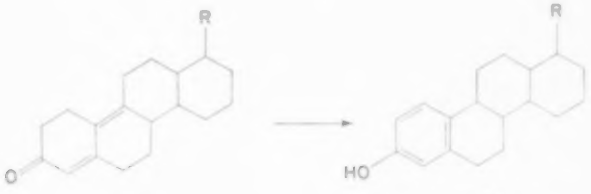
III



IV $R_1 = CO_2Me$, $R_2 = H$
V $R_1 = H$, $R_2 = CO_2Me$



VI $R_1 = CO_2Me$; $R_2 = H$
VII $R_1 = H$, $R_2 = CO_2Me$



VIII IX

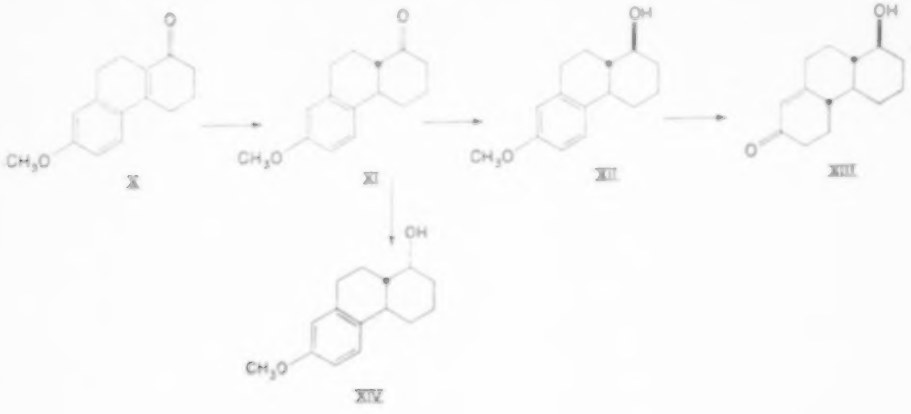
The influence of the double bonds on the relative stabilities of the stereoisomers in the hydrophenanthrene series has not received much attention. The present investigation was started with this aim. It was hoped that the acid-catalysed isomerization of the dienone (VIII) into the phenol (IX) would throw light on the stability orders of the stereoisomers of IX.[16]

The choice of this system was dictated by two reasons: (i) The compounds of type (VIII) were accessible by stereochemically unambiguous routes; (ii) Johnson's work on stereoisomeric oestrones[17] provided ready means of identifying the products.

We report in the present paper, the preparation of two tricyclic intermediates XIII and XVII capable of elaboration to the dienones of type VIII, having the *anti*- and *syn*-backbones respectively. The starting materials for the two series are the *trans*- and *cis*-forms of the octahydrophenanthrone (I), reported by Birch *et al.*[10] by the controlled lithium–ammonia reduction of 1-oxo-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene (X).[18]

[15] E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.* **81**, 5601 (1959).
[16] See also: C. Sannie and J. J. Panouse, *Bull. Soc. Chim.* 1435 (1956).
[17] W. S. Johnson, I. A. David, H. C. Dehm, R. J. Highet, E. W. Warnhoff, W. D. Wood and E. T. Jones, *J. Amer. Chem. Soc.* **80**, 661 (1958).
[18] G. Stork, *J. Amer. Chem. Soc.* **69**, 2936 (1947); F. J. Villani, M. S. King and D. Papa, *J. Org. Chem.* **18**, 1578 (1953).

Reduction of *trans*-1-oxo-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene (XI) by sodium borohydride gave a mixture of epimeric hydroxy compounds, m.p. 102–103° and 92°, in the ratio 2:1. The major product has been assigned the β-configuration (equatorial-OH) (XII)[19] and the other epimer, the α-configuration (axial-OH) (XIV). The configurations assigned were confirmed as follows:[20] The



compound, m.p. 102°, gave a *p*-nitrobenzoate by treatment with *p*-nitrobenzoyl chloride and pyridine at room temperature, whereas the compound, m.p. 92°, did not react even under vigorous conditions; on chromatography over alumina, the compound, m.p. 92°, was eluted first, by petroleum ether–benzene mixture, and the compound, m.p. 102–103°, later by benzene.

Recently Dauben *et al.*[21] have noted that the borohydride reductions are subject to 'steric approach control' to a greater extent than lithium aluminium hydride reductions. While the result obtained by us is fairly in agreement with this view, the formation of a large amount of the axial epimer (ca. 35%) is somewhat surprising. Probably in this case the 'product development control' factor also operates in favour of the axial epimer to a greater extent than in the cases studied by Dauben *et al.*[21]

We next carried out the reduction of the *trans*-ketone (XI) by lithium tri-t-butoxyaluminohydride,[22] which has been reported to be highly stereospecific.[23,24] By using this method the equatorial hydroxy compound (XII), m.p. 102°, was obtained as the single isolable product in ca. 65 per cent yield. Birch reduction, using the Wilds and Nelson's modification,[25] of XII gave the dihydroderivative in high yield, which on acid hydrolysis gave the *trans-anti*-α,β-unsaturated ketone (XIII). Preparation of the dienone of type VIII, from the unsaturated ketone (XIII) is in progress.

Next we turned to the *syn*-series. So far the *syn*-hydrophenanthrenes were only of

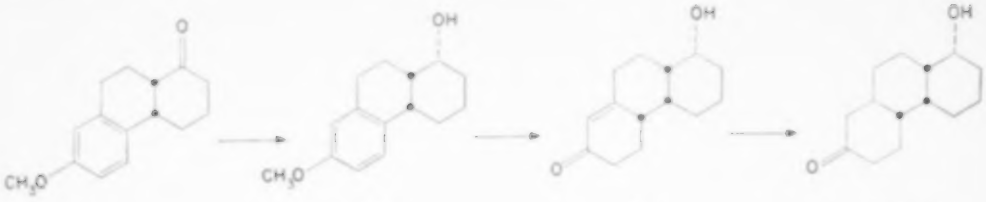
[19] Steroid nomenclature. The hydrogen atom at C_{11} is assumed to be β. The compounds described in this paper are racemic.
[20] D. H. R. Barton, *J. Chem. Soc.* 1027 (1953).
[21] W. G. Dauben, G. J. Fonken and D. S. Noyce, *J. Amer. Chem. Soc.* **78**, 2579 (1956); W. G. Dauben E. J. Blanz, J. Jiu and R. Micheli, *Ibid.* **78**, 3752 (1956).
[22] H. C. Brown and R. F. McFarlin, *J. Amer. Chem. Soc.* **80**, 5372 (1958).
[23] O. H. Wheeler and J. L. Mateos, *Canad. J. Chem.* **36**, 1431 (1958).
[24] J. Fajkos, *Coll. Czech. Chem. Comm.* **24**, 2284 (1959).
[25] A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.* **75**, 5360 (1953).

theoretical interest, but recent work[26–29] has shown that a number of diterpenes have the *syn*-backbone. Presently only two general methods are known for building up such systems. The first takes advantage of the stereospecificity of the Diels–Alder reaction,[30] and the second depends upon the phenomenon of catalyst hindrance observed by Linstead *et al.*[31,32] We have developed a new procedure which makes use of the conformational flexibility of the *cis*-decalin system.[33] The *syn*-compounds prepared by us for the present work are also useful intermediates for the synthesis of diterpenes.

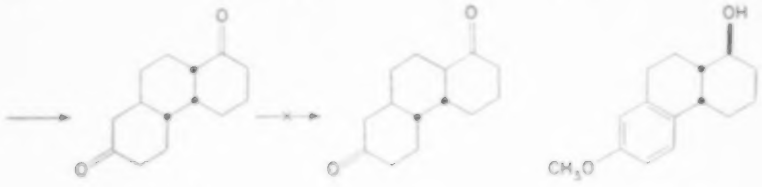
Reduction of *cis*-octahydrophenanthrone (XV)[10] by sodium borohydride gave a single hydroxy compound, which has been assigned the configuration XVI on the following grounds. The *cis*-ketone (XV) could exist in either of the two conformations XXI or XXII and the approach of the reducing hydride species from the concave side of the cage-like structure is highly hindered in both the conformations. Hence XVI appears to be the only reasonable configuration for the reduction product.[34] Reduction of the *cis*-ketone (XV) by lithium tri-t-butoxyaluminohydride was not stereospecific to this extent. Chromatographic separation of the reduction product followed by purification as the *p*-nitrobenzoate showed that the α-hydroxy compound (XVI) was the major product. The other by-product, which must undoubtedly be the epimeric β-hydroxy compound (XXIII) could not be isolated in the pure state. The course of the latter reduction throws some light on the relative stability of the two conformations, XXI and XXII, of the *cis*-ketone (XV). It has been definitely proved by the work of Wheeler and Mateos[23] that the reduction by lithium tri-t-butoxyaluminohydride is subject largely to 'product development control'. With XXII representing the conformation of the *cis*-ketone (XV), the configuration of the reduction product should be (XXIII)[β-OH(e)], whereas the [α-OH(e)] should be derived from the conformation XXI. The isolation of XVI as the major product shows that the *cis*-ketone exists preferentially in the conformation (XXI). This observation is in agreement with the conclusion of Djerassi and Marshall,[35] that *cis*-10-methyl-1-decalone exists preferentially in the conformation XXIV, on the basis of rotatory dispersion measurements.[36]

Next we carried out the lithium–liquid ammonia reduction of the *cis*-1α-hydroxy compound (XVI). The intermediate enol ether (XXV) was isolated in good yield, which on hydrolysis gave the α,β-unsaturated ketone (XVII) in ca. 35 per cent yield together with a considerable amount of the β,γ-unsaturated ketone (XXVI), which could be obtained only in impure condition. The formation of the β,γ-unsaturated ketone is to be attributed to the *cis*-fusion of the C-D rings in XVI. The

[26] E. Wenkert and J. W. Chamberlin, *J. Amer. Chem. Soc.* **81**, 688 (1959).
[27] O. E. Edwards and R. Howe, *Chem. & Ind.* 537 (1959); *Canad. J. Chem.* **37**, 760 (1959).
[28] B. Green, A. Harris and W. B. Whalley, *J. Chem. Soc.* 4715 (1958).
[29] C. Djerassi, M. Cais and L. A. Mitscher, *J. Amer. Chem. Soc.* **81**, 2387 (1959).
[30] P. A. Robins and J. Walker, *J. Chem. Soc.* 3960 (1954) and later papers in the series.
[31] R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine and R. W. Whetstone, *J. Amer. Chem. Soc.* **64**, 1985 (1942) and later papers.
[32a] J. W. Cornforth and R. Robinson, *J. Chem. Soc.* 1855 (1949); [b] W. S. Johnson, J. Ackerman, J. F. Eastham and H. A. DeWalt, Jr., *J. Amer. Chem. Soc.* **78**, 6302 (1956).
[33] For an earlier application of this concept, see R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, *Tetrahedron* **2**, 1 (1958).
[34] For an analogy see L. H. Sarett, R. M. Lukes, G. I. Poos, J. M. Robinson, R. E. Beyler, J. M. Vandegrifft and G. E. Arth, *J. Amer. Chem. Soc.* **74**, 1393 (1952); R. E. Beyler and L. H. Sarett, *Ibid.* **74**, 1406 (1952).
[35] C. Djerassi and D. Marshall, *J. Amer. Chem. Soc.* **80**, 3986 (1958).
[36] The referee has kindly pointed out that examination of scale models also shows that XXI is the preferred alternative.



XV XVI XVII XVIII



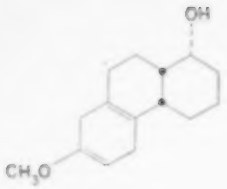
XIX XX XXIII

XXI

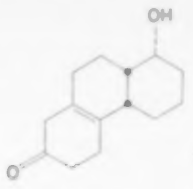
XXII XXIV

configuration XVII, assigned to the α,β-unsaturated ketone is based on the following grounds. The intermediate enol ether (XXV), on hydrolysis, could give rise to the *cis-syn*-unsaturated ketone (XVII) or the corresponding *cis-anti*-isomer (XXVII). It is possible for XVII to exist in an all-chair conformation (XXVIII) in which the hydroxyl group is equatorial. On the other hand two conformations are possible for the *cis-anti*-isomer (XXVII), (XXIXa and b), both of which are energetically unfavourable. The former contains a 1:3-diaxial OH . . . . CH interaction. Conformation XXIXb, having the C-ring in the boat form, is derived from XXIXa by an inversion of the *cis*-decalin part through the intermediacy of XXIXc in which C_5 is axially oriented with respect to ring-C. It should be emphasized that it is not possible to attach ring-B with the α,β-unsaturated ketonic group, if C_5 is axial. Hence ring-C is forced into a boat conformation as in XXIXb. Thus the *cis-syn*-configuration (XVII) appears to be energetically the most favoured one.

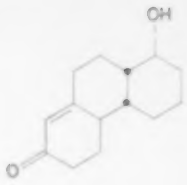
The configuration assigned to the tricyclic ketone (XVII) has been confirmed as follows: Reduction of XVII by lithium–liquid ammonia procedure gave the BCD-*trans-syn-cis* saturated hydroxy ketone (XVIII) which was oxidised by chromium



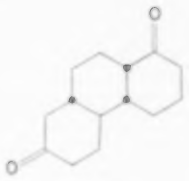
XXV



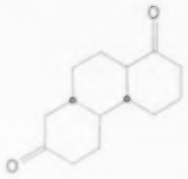
XXVI



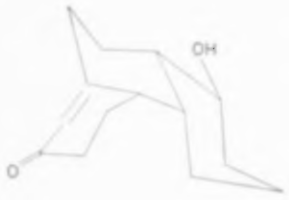
XXVII



XXX



XXXI



XXVIII

XXIX a

XXIX b

XXIX c

trioxide in pyridine to the *cis-syn-trans*-diketone (XIX). As expected, this did not undergo isomerization on treatment with alkali, because the isomerization product, the *trans-syn-trans*-diketone, is known to be thermodynamically less stable than (XIX).[3] If the unsaturated ketone had the *cis-anti*-configuration (XXVII) the configuration of the derived diketone would be XXX (BCD-*trans-anti-cis*). This would be expected to undergo easy isomerization to the more stable *trans-anti-trans* configuration (XXXI).

Further experiments are in progress to add the A-ring to the enone (XVII) and also to convert it into the isopimaric acid group of diterpenes.

EXPERIMENTAL[27]

trans-anti-Series

Reduction of trans-1-*oxo*-7-*methoxy*-1,2,3,4,9,10,11,12-*octahydrophenanthrene* (xi)

(a) *By sodium borohydride*. To a solution of *trans*-1-oxo-7-methoxy-1,2,3,4,9,10,11,12,-octahydrophenanthrene (XI)[16] (460 mg) in methanol (20 ml) was slowly added a solution of sodium borohydride (380 mg) in water (5 ml). There was a vigorous reaction and after standing for 10 hr at room temp, the mixture was poured into iced dil. HCl. The aqueous solution on standing deposited a white crystalline solid, m.p. 63–68°, yield 280 mg. Separation of this mixture into the epimeric hydroxy compounds XII and XIV was achieved by two methods:

(i) Fractional crystallization from pet ether gave first trans-1β-*hydroxy*-7-*methoxy*-1,2,3,4,9,10,11,12-*octahydrophenanthrene* (XII) as feathery needles, m.p. 102–103°; yield 90 mg; infra-red absorption, 3650 cm^{-1} (OH). (Found: C, 77·52; H, 8·74. $C_{15}H_{20}O_2$ requires: C, 77·59; H, 8·62%).

The mother liquors yielded a solid which on further crystallization from the same solvent furnished colourless stout rods of trans-1α-*hydroxy*-7-*methoxy*-1,2,3,4,9,10,11,12-*octahydrophenanthrene* (XIV), m.p. 92°; yield 30 mg; infra-red absorption, 3675 cm^{-1} (OH). (Found: C, 78·02; H, 8·7. $C_{15}H_{20}O_2$ requires: C, 77·59; H, 8·62%).

(ii) The crude reduction product (170 mg) was chromatographed over Merck's alumina (5 g). Elution with 1:1 pet ether–benzene mixture (40 ml) gave the crude *trans*-1α-hydroxy compound(XIV), m.p. 85–91°; after crystallization it melted at 92°; yield 50 mg. Elution with solvent mixtures containing increasing proportions of benzene gave non-crystalline product (35 mg). Elution with benzene gave the *trans*-1β-hydroxy compound (XII), m.p. 90–100°; after crystallization m.p. 102–103°; yield 75 mg.

p-*Nitrobenzoylation of* XII *and* XIV. A mixture of the equatorial hydroxy compound (XII), m.p. 102–103°, (8·0 mg) and *p*-nitrobenzoyl chloride (8·5 mg) was dissolved in pyridine (2 drops) and left overnight at room temp. The mixture was poured into water and extracted with ether. The extract was washed with dil HCl, water, dil NaOH and water and dried (Na_2SO_4). Removal of the solvent gave 1β-p-*nitrobenzoyloxy*-7-*methoxy*-1,2,3,4,9,10,11,12-*octahydrophenanthrene* (6·1 mg) as fine feathery needles, m.p. 104°, after crystallization from ether–pet ether mixture. Crystallization from benzene–pet ether mixture gave a different polymorph as stout rods, m.p. 148–150°. (Found: N, 3·50. $C_{22}H_{23}O_4N$ requires: N, 3·67%).

The epimeric hydroxy compound (XIV), m.p. 92°, (9·0 mg) on similar treatment was recovered unchanged after a reaction period of 30 hr at room temp. When the reaction was carried out at 80° for 40 min only an oily product was obtained.

(b) *By lithium tri-t-butoxyaluminohydride*. t-Butanol (2·5 ml) was added with stirring to a suspension of lithium aluminium hydride (500 mg) in purified diglyme or tetrahydrofuran (25 ml) maintained below 0° in an ice-salt bath. The *trans*-ketone (XI, 490 mg) in diglyme or tetrahydrofuran was added with stirring to the turbid solution of the hydride at 0°. The mixture was stirred at 0° for 30 min and at room temp for 1 hr. On acidification with iced dil HCl (500 ml), a white precipitate (300 mg) was obtained, m.p. 102–103°, undepressed by admixture with the product XII from the borohydride reduction.

Trans-anti-1β-*Hydroxy*-7-*oxo*-$\Delta^{9(14)}$-*dodecahydrophenanthrene* (XIII). To a stirred solution of lithium (590 mg) in anhydrous liquid ammonia (200 ml) was added a solution of *trans*-1β-hydroxy-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene (XII) (325 mg) in anhydrous ether (20 ml). The mixture was stirred for 5 min and anhydrous ethanol (5 ml) was added dropwise during ca 3 min. The solution was stirred till the blue colour disappeared. Ammonia was allowed to evaporate and water was added to the reaction mixture. On letting the mixture stand for 1 hr, a colourless precipitate of trans-1β-*hydroxy*-7-methoxy-1,2,3,4,5,8,9,10,11,12-*decahydrophenanthrene* was obtained; m.p. 124–126°; yield 280 mg. The above dihydro-derivative in the crude state was hydrolysed by refluxing with methanol (14 ml) and 3N HCl (8 ml) under nitrogen for 45 min and then poured onto ice (300 g). The aqueous solution was saturated with $(NH_4)_2SO_4$ and extracted with a mixture of ether and pet ether.

[27] All melting points are uncorrected. U.V. spectra were measured in 95% ethanol. Petroleum ether used in this section had b.p. 40–60°. Microanalyses were carried out by Messrs. B. R. Seetharamia and D. P. Bose of this department.

The extract was washed with brine, ice-cold 2% NaOH solution, brine and a little water and dried (Na_2SO_4). Evaporation of the solvent under vacuum at 30° gave *trans-anti*-1*β*-hydroxy-7-oxo-$\Delta^{8(14)}$-dodecahydrophenanthrene (XIII), m.p. 140–155°; yield 240 mg. After several crystallizations from ether the product melted at 157–158°. A sample was sublimed for analysis. Infra-red absorption, 3650, 1667, 1613 cm^{-1}; λ_{max} 240 mμ; ε 15,240. (Found: C, 76·03; H, 9·19. $C_{14}H_{20}O_2$ requires: C, 76·36; H, 9·09%).

The 2,4-*dinitrophenylhydrazone* was obtained as a red crystalline powder by Shine's procedure[28] and recrystallized from ethylacetate, m.p. 195–198° (Found: N, 13·72. $C_{20}H_{24}O_5N_4$ requires: N, 13·99%).

The *semicarbazone* was prepared by the sodium acetate procedure, m.p. 246–249° (decomp) after recrystallization from aqueous alcohol. (Found: N, 15·19. $C_{15}H_{23}O_2N_3$ requires: N, 15·15%).

cis-syn-Series

Sodium borohydride reduction of cis-1-*oxo*-7-*methoxy*-1,2,3,4,9,10,11,12-*octahydrophenanthrene* (XV).

The reduction was carried out as described before for the *trans*-compound (XI) using the *cis*-ketone (XV, 110 mg) in methanol (10 ml) and sodium borohydride (200 mg) in water (5 ml). cis-1α-*Hydroxy*-7-*methoxy*-1,2,3,4,9,10,11,12-*octahydrophenanthrene* (XVI) (63·9 mg), m.p. 85–89°, was thus obtained. On recrystallization from ether–pet ether mixture it came out as colourless plates, m.p. 94–96°; mixed m.p. with the *trans*-1α-hydroxycompound (XIV), m.p. 92°, was depressed. In other experiments a different polymorph of (XVI), m.p. 81–83°, was also obtained. The polymorphic relationship was established by melting the lower melting form and seeding it with the higher melting one at 85°, when it resolidified and melted again at 92–96°. Both forms gave the same *p*-nitrobenzoate. A sample was sublimed for analysis at 75° (1 mm). Infra-red absorption, 3680 cm^{-1} (OH). (Found: C, 77·34; H, 8·67. $C_{15}H_{20}O_2$ requires: C, 77·59; H, 8·62%).

The *p*-nitrobenzoate of *cis*-1α-hydroxy-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene (XVI) was prepared by the previously described procedure. Crystallization from benzene–pet ether gave fine needles, m.p. 148–150°; mixed m.p. with the *p*-nitrobenzoate of XII was depressed (Found: N, 3·53. $C_{22}H_{23}O_5N$ requires: N, 3·67%).

Lithium tri-t-butoxyaluminohydride reduction of the cis-*ketone* (XV)

Reduction of the *cis*-ketone (XV, 230 mg) in tetrahydrofuran (5 ml) was carried out with lithium tri-t-butoxyaluminohydride prepared from lithium aluminium hydride (210 mg) and t-butanol (1 ml) in tetrahydrofuran (9 ml) by the procedure described above for the *trans* ketone (XI). The oily product, thus obtained, was chromatographed over alumina (6 g). Elution with 3:1 benzene–pet ether mixture gave a low melting product, m.p. ca. 65° (73mg). This gave a *p*-nitrobenzoate (62·0 mg) by the usual procedure, m.p. 115–135°, raised by further crystallization from benzene–pet ether mixture to 148–150°, undepressed by admixture with the *p*-nitrobenzoate of the borohydride reduction product. Elution with ether gave a crystalline solid (75 mg), m.p. 80°, undepressed by admixture with the borohydride reduction product. It gave a *p*-nitrobenzoate, m.p. 145–148°, identical with that reported above.

cis-syn-1α-*Hydroxy*-7-*oxo*-$\Delta^{8(14)}$-*dodecahydrophenanthrene* (XVII)

Reduction of *cis*-1α-hydroxy-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene (XVI, 1·05 g) in ether (25 ml) was carried out with lithium (2·1 g) in anhydrous liquid ammonia (300 ml) and alcohol (17·5 ml) as described before and cis-1α-*hydroxy*-7-*methoxy*-1,2,3,4,5,8,9,10,11,12-*decahydrophenanthrene* (XXV, 950 mg) thus obtained was directly hydrolysed with refluxing methanol (43 ml) and 3N HCl (15 ml) under nitrogen for 20 min. The product was worked up as before and the resulting crude oily product on maceration with ether gave *cis-syn*-1α-hydroxy-7-oxo-$\Delta^{(8)14}$-dodecahydrophenanthrene (XVII, 340 mg), m.p. 136–139°. After recrystallization from ether it melted at 138–140°. A sample was sublimed for analysis at 130° (1 mm). Infra-red absorption: 3704 cm^{-1} (OH); 1664 cm^{1} (α,β-unsaturated ketone); λ_{max} 241 mμ; ε 17,280 (Found: C, 76·60; H, 9·11. $C_{14}H_{20}O_2$ requires: C, 76·36; H, 9·09%).

The 2,4-*dinitrophenylhydrazone* was obtained as shiny red needles from ethyl acetate, m.p. 181–182° (Found: N, 13·96. $C_{20}H_{24}O_5N_4$ requires: N, 13·99%).

[28] H. J. Shine, *J. Org. Chem.* **24**, 252 (1959).

The mother liquors from the α,β-unsaturated ketone gave a crystalline solid, m.p. 105–125° (150 mg) which showed no absorption maximum in the ultra-violet region. The product, in all probability, is the *β,γ-unsaturated ketone* (XXVI).

cis-syn-trans-1α-*Hydroxy*-7-*oxo-perhydrophenanthrene* (XVIII)[20]

To a solution of lithium (14·7 mg) in anhydrous liquid ammonia was added a solution of *cis-syn*-1α-hydroxy-7-oxo-$\Delta^{9(14)}$-dodecahydrophenanthrene (XVII), 113 mg) in anhydrous ether and the mixture stirred till the blue colour disappeared. Ice-cold water was cautiously added and the aqeous solution extracted with ether. The extract was washed with water and dried (Na_2SO_4). Removal of solvent gave *cis-syn-trans*-1α-hydroxy-7-oxoperhydrophenanthrene (XVIII, 76·6 mg) m.p. 145–151°, raised to 152–154° after two crystallizations from benzene–pet ether mixture. A sample was sublimed for analysis at 140° (1 mm). Ultra-violet spectrum showed the absence of any α,β-unsaturated ketone $\varepsilon_{286}39$; infra-red absorption 3680 cm^{-1} (OH) and 1701 cm^{-1} (C=O) (Found: C, 75·43; H, 10·02. $C_{14}H_{22}O_2$ requires: C, 75·65; H, 9·91%).

cis-syn-trans-1,7-*Dioxo-perhydrophenanthrene* (XIX)[10]

To the complex of chromium trioxide (127 mg) and pyridine (1·2 ml) was added a solution of *cis-syn-trans*-1α-hydroxy-7-oxo-perhydrophenanthrene (XVII, 70 mg) in pyridine (1·2 ml). The solution, which darkened immediately, was allowed to stand overnight at room temp and then poured into water (150 ml) followed by acidification with 10% H_2SO_4 (50 ml). The aqueous solution was extracted with ether–pet ether mixture. The extract was washed with water, saturated $NaHCO_3$ solution, water and dried (Na_2SO_4). Evaporation of the solvent at room temp under vacuum gave *cis-syn-trans*-1,7-dioxoperhydrophenanthrene (XIX, 35 mg), m.p. 93–98°. After recrystallization from pet ether it melted at 97–98°. Infra-red absorption, 1700 cm^{-1} (C=O) (Found: C, 75·96; H, 9·19. $C_{14}H_{20}O_2$ requires: C, 76·36; H, 9·09%).

Stereochemical stability of cis-syn-trans-1,7-*dioxoperhyrophenanthrene* (XIX)

The diketone (XIX, 9·0 mg), m.p. 97–98°, was refluxed with 2% methanolic KOH (5 ml) under nitrogen for 30 min. The solvent was removed under reduced press and water (25 ml) was added. The aqueous solution was saturated with $(NH_4)_2SO_4$ and extracted with ether–pet ether mixture. The extract was washed with water and dried (Na_2SO_4). Removal of the solent under reduced press and crystallization of the residue from pet ether gave the starting diketone (XIX, 3·0 mg), m.p. 95–98°, either alone or on admixture with starting diketone(XIX), m.p. 97–98°. The low recovery is probably due to some decomposition taking place on alkali treatment.

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[20] Procedure of D. K. Banerjee, S. Chatterjee and S. P. Bhattacharyya, *J. Amer. Chem. Soc.* **77**, 404 (1955).
[10] Procedure of G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *J. Amer. Chem. Soc.* **75**, 423 (1953).

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ISOLEMENT ET STRUCTURE D'UN NOUVEAU DITERPÈNE: L'ACIDE DANIELLIQUE

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STÉRÉOCHIMIE DE L'ACIDE DANIELLIQUE

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Résumé—Les propriétés spectrales, la déshydrogénation et l'ozonisation de l'acide daniellique, diterpène de *Daniellia oliveri* (Césalpiniée), permettent de lui attribuer la formule (I). La stéréochimie absolue indiquée sur cette formule découle d'une corrélation avec l'acide agathique.

Abstract—A new diterpene acid, daniellic acid, has been isolated from the African copal tree, *Daniellia oliveri* (Caesalpineae). Structure (I) is demonstrated for daniellic acid; the stereochemistry implied (relative and absolute) is derived from a correlation with agathic acid.

LA Césalpiniée africaine, *Daniellia oliveri*,* fournit une oléorésine constituée par un mélange de sesquiterpènes et d'un acide diterpénique, en proportion variable avec l'âge de l'arbre et le nombre de gemmages qu'il a subis précédemment. Il y a quelques années, Criqui[1] décrivait l'isolement de cet acide diterpénique, apparemment nouveau. Il proposait la formule $C_{20}H_{28}O_3$, reconnaissait la présence de trois doubles liaisons hydrogénables, et postulait pour l'atome d'oxygène non-acide une fonction éther.

Une nouvelle étude de l'acide, que nous appellerons désormais daniellique, nous a conduits à lui attribuer la structure[2] et la stéréochimie absolue indiquées par la formule (I)

Isolement de l'acide daniellique (J. H., R. L.)

Une grande partie de l'acide daniellique contenu dans l'oléorésine brute cristallise spontanément. Il est utile, pour en faciliter l'isolement, de commencer par préparer le sel de diéthylamine; l'acide ultérieurement régénéré est recristallisé dans le méthanol. L'acide daniellique présente les constantes suivantes: $F = 129–130{\cdot}5°$; $[\alpha]_j = -58°$. Son sel de diéthylamine est cristallisé [$F = 122°$; $[\alpha]_j = -20°$], mais son ester méthylique n'a été obtenu que liquide.

Structure de l'acide daniellique (J. H., R. L.)

La structure de l'acide daniellique découle des faits suivants:

—La formule $C_{20}H_{28}O_3$ a été confirmée directement, par dosage des trois éléments de l'acide et des quatre du sel de diéthylamine. Elle découle également de la suite des dégradations.

* L'identification botanique de ce copalier de l'Oubangui-Chari a été faite par le Service des Eaux, Forêts et Chasses de ce territoire.

[1] A. Criqui, Thèse d'Ing. Docteur, Strasbourg (1956).
[2] J. Haeuser, *Bull. Soc. Chim. Fr.* 1447 (1959).

—La présence de trois doubles liaisons a été confirmée par hydrogénation catalytique; le produit hexahydrogéné n'a pas pu être amené à cristalliser, et il n'a pas été possible de réaliser des hydrogénations sélectives.

Une des doubles liaisons constitue un groupe vinylidène: le spectre I. R. de l'acide daniellique présente les bandes caractéristiques de ce groupe: $\delta(C{=}CH_2)$ 890 cm^{-1}, et $\nu(C{=}CH_2)$ 1645 cm^{-1}. En outre, l'ozonisation fournit du formaldéhyde (isolé par sa combinaison avec la dimédone); l'ozonisation quantitative selon Naves et Doeuvre[3,4] donne une quantité de formol équivalente à celle que fournit l'acide agathique (V).

Les deux autres doubles liaisons sont présentes dans un cycle furannique, qui rend également compte de la nature du troisième atome d'oxygène. Le spectre U.V. de l'acide daniellique (λ_{max} 225 mμ; $\varepsilon = 1650$) et son spectre I.R. (873, 1022, 1065, 1170, 1241, 1495, 1558, 1600 cm^{-1})[5] indiquent la présence d'un tel noyau furannique, qui est confirmée par le spectre de résonance magnétique nucléaire du daniellate de méthyle: ce spectre montre les bandes caractéristiques d'un furanne β-substitué: deux Hα sont présents, et un Hβ, aux positions attendues.[6]

Le reste du spectre est en accord avec les conclusions précédemment déduites; il montre d'autre part la présence dans le squelette de *deux* groupes méthyles, tous deux portés par des atomes de carbone complètement substitués (absence de dédoublement par interaction spin–spin). Ces deux groupes méthyles sont très nettement séparés (26 cps à 40 mc), ce qui semble impliquer que l'un est axial, l'autre équatorial.

Les éléments fonctionnels ainsi définis exigent, avec la formule brute de l'acide daniellique, une structure contenant *deux* cycles carbonés. En effet, la déshydrogénation de l'acide daniellique par le sélénium donne un triméthylnaphtalène, probablement le triméthyl-1,2,5 naphtalène (agathalène), identifié par le point de fusion de son picrate.[7]

Tenant compte de la règle isoprénique, ces résultats permettent de proposer comme probable la formule (I) pour l'acide daniellique, à la stéréochimie près; cette formule a effectivement été entièrement justifiée (voir ci-dessous).

Notons que la saponification du daniellate de méthyle est très difficile; le groupe acide est donc probablement *axial*.

Stéréochimie de l'acide daniellique (F. L., G. O.)

La structure proposée pour l'acide daniellique a été confirmée, et sa stéréochimie relative et absolue a été précisée, par une corrélation avec l'acide agathique.* La formule (I) en résulte.

L'ozonisation de l'acide daniellique donne le diacide cétone (II), F = 190°. De même, l'ozonisation du daniellate de méthyle donne un acide-ester-cétone (III), que nous n'avons pas obtenu cristallisé, mais qui donne un ester de *p*-phénylphénacyle (IV) cristallisé, F = 140°.

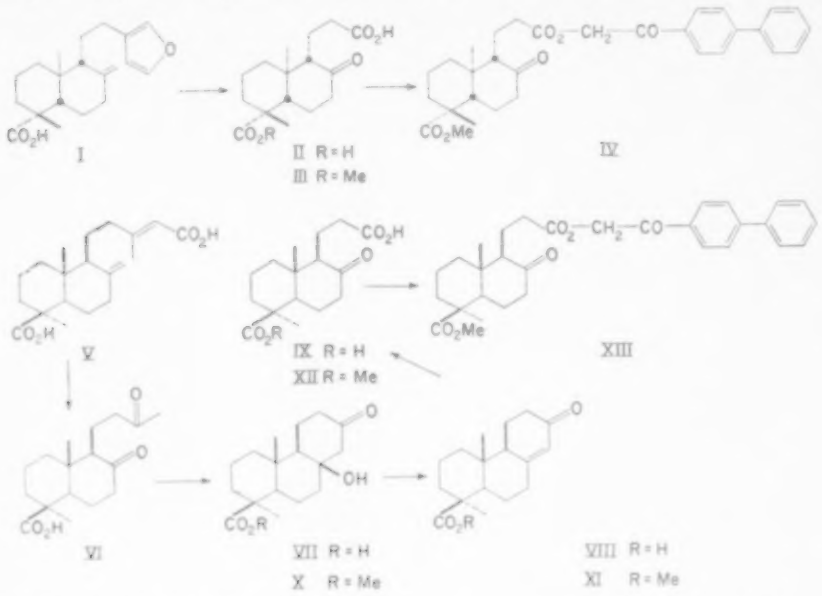
Des produits de même structure plane, *mais de configuration opposée*, ont été

* La stéréochimie absolue de l'acide agathique a été établie par corrélation chimique (*cf.*[8]).

[3] J. Doeuvre, *Bull. Soc. Chim. Fr.* 612 (1936).
[4] Y. R. Naves, *Helv. Chim. Acta* **32**, 1151 (1949); cf. Y. R. Naves et R. Ardizio, *Bull. Soc. Chim. Fr.* 299 (1953).
[5] T. Kubota, *Tetrahedron* **4**, 68 (1958); M. Fétizon, publication en cours.
[6] E. J. Corey, G. Slomp, Sukh Dev, S. Tobinaga et R. Glazier, *J. Amer. Chem. Soc.* **80**, 1204 (1958).
[7] L. Ruzicka et J. R. Hosking, *Helv. Chim. Acta* **13**, 1402 (1930).
[8] L. Ruzicka et E. Bernold, *Helv. Chim. Acta* **24**, 931, (1941); L. Ruzicka, R. Zwicky et O. Jeger, *Ibid.* **31**, 2143 (1948).

préparés à partir de l'acide agathique (V). Ce dernier, par ozonisation, donne l'acide-dicétone (VI), F = 138°, aisément isomérisable en cétol (VII) F = 264° lui-même déshydratable en cétone α,β-éthylénique (VIII) F = 190°.

L'ozonisation de cette dernière donne le diacide cétonique F = 191°, (IX), *a priori* identique à (II), ou antipode, ou épimère. La même suite de réactions réalisée sur



l'ester méthylique de l'acide agathique[9] donne, comme précédemment, un acide-ester-cétone (XII) non cristallisé, caractérisé par son ester de *p*-phénylphénacyle (XIII) F = 141° *a priori* identique à (IV), ou antipode, ou épimère.

Les deux paires de composés (II) et (IX), et (IV) et (XIII), sont en fait *antipodes*. Ceci résulte:

—de *l'identité* de leurs constantes physiques: point de fusion, spectre d'absorption infra-rouge (Fig. 1),

—de *l'identité* des diagrammes de poudre sur (II) et (IX), pris avec la raie $K\alpha$ du cuivre (Fig. 2),

—mais du *signe opposé* de leurs pouvoirs rotatoires, dans tout le domaine spectral accessible (600–260 mμ pour les premiers, 600–350 mμ pour les seconds) (Fig. 3).

La structure (I) est ainsi démontrée complètement. Elle constitue un hybride des structures de plusieurs diterpènes, présentant divers caractères relativement rares: groupe acide *axial* en C-4 (comme dans les acides podocarpique et agathique), chaîne furannique (comme dans la marrubiine et la columbine), configuration absolue "anormale", inverse de celle de l'acide abiétique (comme dans l'acide épéruique, le cafestol, etc.).

PARTIE EXPERIMENTALE

Les spectres U.V. ont été mesurés avec un spectrophotomètre Unicam S.P. 500; les spectres I.R., avec un spectrophotomètre Perkin-Elmer 21 à optique de NaCl; les dispersions rotatoires, avec un

[9] L. Ruzicka, E. Bernold et A. Tallichet, *Helv. Chim. Acta* **24**, 223 (1941).

spectropolarimètre Rudolf; les spectres de R.M.N., avec un appareil Varian fonctionnant à 40 mc.

Les microanalyses ont été faites par le Service Central de Microanalyse du C.N.R.S., à l'Ecole Normale Supérieure ("E.N.S.") et à la Faculté des Sciences de Lyon ("Lyon").

L'isolement de l'acide daniellique, et une caractérisation préliminaire, ont été décrits dans la thèse d'Ingénieur-Docteur de A. Criqui[1].

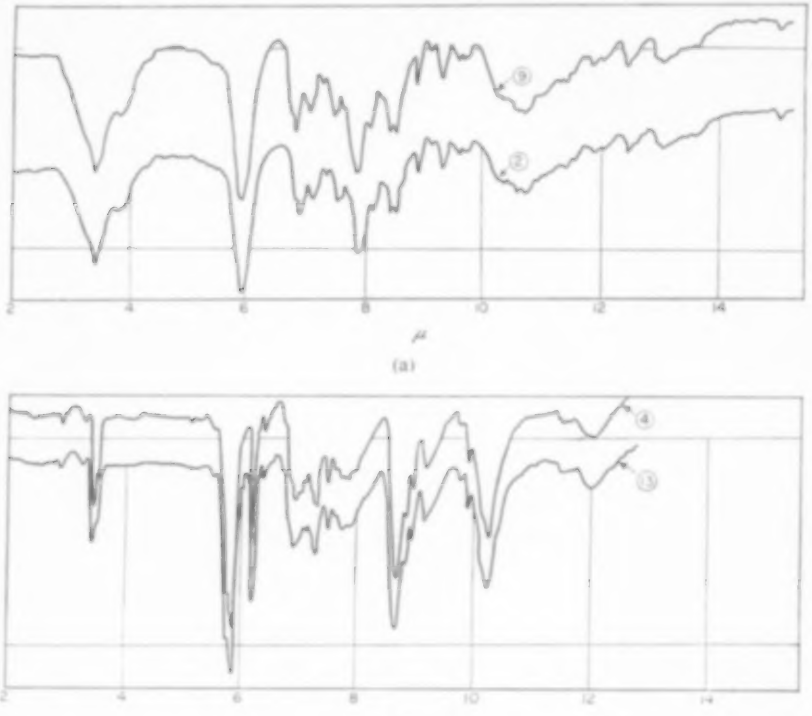


FIG. 1. Spectre infra-rouge des antipodes 2 et 9 (1a), et 4 et 13 (1b) (pastilles de KBr).

Isolement de l'acide daniellique (J. H.)

L'oléorésine de *Daniellia oliveri*, obtenue par saignée profonde et excitation par le feu de l'exsudation, a l'aspect d'une gemme de pin. Une fraction liquide importante (A) est séparée par décantation; il reste une fraction cristallisée (B) imprégnée d'huile, et constituée d'acide daniellique impur. La fraction liquide (A) fournit, par entraînement à la vapeur ou distillation sous pression réduite, des matières volatiles (sesquiterpènes non identifiés), et une colophane cristallisable dans le méthanol, constituée essentiellement d'acide daniellique.

Le dépôt cristallin (B), dont l'essorage est difficile, est dissous dans l'acétone. Après filtration, on ajoute une quantité à peu près stoechiométrique de diéthylamine diluée dans trois fois son volume d'acétone. La réaction est exothermique, et au refroidissement le sel cristallise en aiguilles. Le produit est essoré, lavé avec très peu d'acétone froide, et dissous à chaud dans le volume minimum d'éthanol. On ajoute de l'acide acétique aqueux à 2%, en quantité stoechiométrique. L'acide daniellique cristallise au refroidissement. Trois recristallisations dans le méthanol donnent l'acide pur.

Acide daniellique (I) (J. H.)

Les cristaux ont la forme de plaquettes hexagonales. Par évaporation très lente d'une solution alcoolique d'acide daniellique on obtient des cristaux rhomboédriques à troncature perpendiculaire à l'axe ternaire.

VOL.
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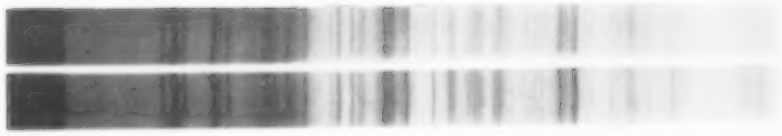

FIG. 2. Diagramme de diffraction de rayons X des antipodes 2 et 9 (raie $K\alpha$ du cuivre).

VOL
12
196

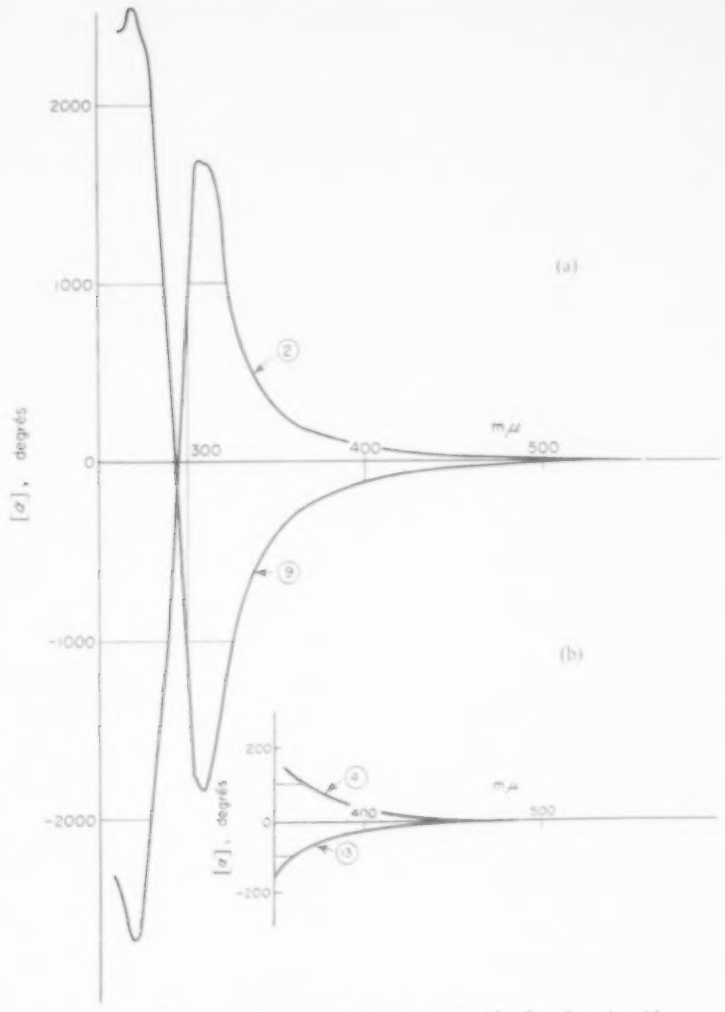

FIG. 3. Dispersion rotatoire des antipodes 2 et 9, et 4 et 13.

F_{cor} = 129–130·5° (cap).
$C_{20}H_{28}O_3$ (316·4) Calc.%: C 75·91 H 8·92 O 15·17
Tr.: C 76·2 H 8·9 O 15·2 (E.N.S.)

Masse moléculaire (acidimétrie): 313; dosage de doubles-liaisons (acide perbenzoïque 0·2 N dans le chloroforme): 3,3 équivalents.

Spectre U.V.: λ_{max} 225 mμ (ε = 1650; heptane) (furanne[3])

Spectre I.R.: 873, 1022, 1065, 1170, 1241, 1495, 1558, 1600 cm^{-1} (furanne β-substituée[3]).

D.R.: Dispersion simple négative: $[\alpha]_{600}$ −54°; $[\alpha]_{589}$ −58°; $[\alpha]_{260}$ −258°. (c=1; EtOH)

Sel de diéthylamine

Recristallisé dans l acétone.

F = 120–122°; $[\alpha]_{578}$ −20°.
$C_{24}H_{39}O_3N$ (389·6) Calc.%: C 73·99 H 10·09 O 12·32 N 3·60
Tr.: C 74·65 H 10·1 O 12·4 N 3·6 (E.N.S.)

On obtient aussi des sels cristallisés avec l'ammoniac, la pyridine, la cyclohexylamine. Une combinaison cristallisée est également obtenue avec l'acide ferrocyanhydrique.

Daniellate de méthyle

Obtenu par action du diazométhane, l'ester méthylique est liquide, et n'a pas été caractérisé davantage. L'ester méthylique est quantitativement récupéré intact après 48 hr de reflux dans 20 équivalents de potasse alcoolique 2 N.

RMN du daniellate de méthyle (G. O.)

Le spectre de résonance magnétique nucléaire du daniellate de méthyle a été mesuré à 40 Mc, en solution à environ 20% dans le deutérochloroforme, avec le chlorure de méthylène comme référence interne. La position des bandes obtenues est indiquée ci-dessous en cps par rapport au chlorure de méthylène, et en τ. (*cf.*[19], pour des spectres de RMN sur divers acides diterpéniques).

cps	τ	Nombre de protons	Aspect	Interprétation
−79·2	2·2	2 H	multiplet	Hα furannique
−37·8	3·25	1 H	multiplet	Hβ furannique
17·7	4·64	1 H	ligne large	$>C=CH_2$
30·4	4·96	1 H	ligne large	$>C=CH_2$
69·5	5·94	3 H	ligne fine	$R-CO_2-CH_3$
168	8·4	3 H	ligne fine	$CH_3-C<$
194	9·05	3 H	ligne fine	$CH_3-C<$

Ce spectre a été mesuré lors d'un séjour à l'Université d'Illinois, Urbana, Ill.; nous remercions le Professeur E. J. Corey pour son aide à ce sujet.

Hydrogénation catalytique de l'acide daniellique

Solvant: éthanol ou acide acétique; catalyseur: platine sur charbon, 5%; température et pression ordinaire; 3 moles d'hydrogène absorbées en 3 hr. Le produit n'a pas pu être cristallisé. Le palladium sur charbon et le nickel de Raney n'ont pas permis d'hydrogénation sélective.

Déshydrogénation de l'acide daniellique (J. H.)

On chauffe 30 g d'acide daniellique avec 30 g de sélénium, pendant 40 hr, en élevant la température peu à peu jusqu'à 300°. Après refroidissement, le produit est extrait à l'éther, et l'extrait est distillé sur sodium sous 12 mm. On recueille environ 2 ml d'huile, Eb_{12} 140–160°, que l'on traite à chaud par une solution alcoolique d'acide picrique (0·5 g). En refroidissant à −15°, on obtient 0·3 g de picrate jaune orangé, F = 115–120°. Après 6 recristallisations dans l'éthanol, le point de fusion reste constant. Il s'agit vraisemblablement du picrate du triméthyl-1,2,5 naphtalène, mais une comparaison directe n'a pas été possible.

F = 139–140°
$C_{19}H_{17}O_7N_3$ (399·35) Calc.%: C 57·14 H 4·29 N 10·52
Tr.: C 57·3 H 4·4 N 10·4 (E.N.S.)
[Litt.: F = 137–138°[7]]

Ozonisation de l'acide daniellique

(a) *Dosage du groupe* $C=CH_2$ *selon Doeuvre-Naves*[3] (J.H.) On dissout 3·1 mg d'acide daniellique (10^{-2} mmole) dans 3 ml d'un mélange acide acétique-acétate d'éthyle (2:3). On ozonise à 0° pendant 2 min, par un courant d'oxygène ozonisé à 70 mg/l., avec un débit de 100 ml/min. On verse dans 30 ml de réactif de Schiff, on ajoute 15 ml d'acide chlorhydrique concentré, et on complète à 100 ml

[19] J. C. W. Chien, *J. Amer. Chem. Soc.* **82**, 4762 (1960).

par de l'eau. On opère de même avec 3·3 mg d'acide agathique (10^{-3} mmole), et on prépare dans les mêmes conditions un essai à blanc. On lit ensuite les densités optiques, sous 1 cm, à 595 mμ, par rapport à l'essai à blanc. L'acide daniellique ozonisé donne une lecture de 0·470; l'acide agathique (1C═CH_2), une lecture de 0·489.

(b) *Isolement de la combinaison dimédonique du formaldéhyde* (J. H.) On ozonise 1 g d'acide daniellique dans 20 ml d'acide acétique à 15°, pendant une heure, par un courant d'oxygène ozonisé à 70 mg/l., avec un débit de 200 ml/min.

La solution est ensuite chauffée à reflux pendant une heure, puis additionnée de 5 fois son volume d'eau, lavée à l'éther, et traitée par une solution aqueuse de dimédone (1 g). Après 24 hr le précipité est essoré et recristallisé dans l'éthanol aqueux. F = 189°, pas abaissé par mélange avec le dérivé authentique du formaldéhyde.

(c) *Ozonisation préparative* (F.L.). On ozonise 600 mg d'acide daniellique dans 30 ml de chlorure de méthylène et 3 ml de pyridine, à −70° (méthode de Conia et Leriverend[11]). Après retour à la température ordinaire, on évapore le chlorure de méthylène sous vide, à froid. On ajoute quelques ml d'eau, 10 ml d'eau oxygénée à 30%, et 10 ml de potasse aqueuse à 10%. Après repos de 48 hr, on isole de la manière habituelle la fraction acide (373 mg) qui cristallise par trituration avec de l'éther de pétrole contenant un peu d'éther: F = 168° (Kof.). On chromatographie sur 23 g d'acide silicique (colonne préparée avec éther de pétrole, produit mis en solution dans le minimum d'éther). Le mélange éther de pétrole-éther (4:6) élue le diacide-cétone (II):

F = 190° (Kof.)
$C_{16}H_{28}O_5$ (296·35) Calc.%: C 64·84 H 8·16
Tr.: C 64·8 H 8·0 (Lyon)

Spectre U.V.: λ_{max} 283 mμ (ε = 32; EtOH).
Spectre I.R.: Fig. 1(a).
D.R.: Effet Cotton positif $[\alpha]_{600}$ −37°, $[\alpha]_D$ −35°, $[\alpha]_{500}$ −2°, $[\alpha]_{400}$ +75°, $[\alpha]_{307\cdot5}$ +1688°, $[\alpha]_{300}$ +620°, $[\alpha]_{270}$ −2674°, $[\alpha]_{260}$ −2328° (*c* = 0·19, MeOH) (Fig. 2a).

Formation de l'ester de méthyle et de p-*phénylphénacyle* (IV) (F.L.)

Le diacide-cétone (II) est estérifié au diazométhane. Après chromatographie sur alumine et échec des essais de cristallisation, on saponifie la fonction ester primaire (450 mg, reflux dans 15 ml de méthanol avec 230 mg de potasse, 75 min).

Nous n'avons pas non plus pu cristalliser le monoester, même après chromatographie sur acide silicique.

A 150 mg de monoester méthylique (III), dans 0·5 ml d'eau contenant 22 mg de carbonate de sodium, on ajoute de l'acide chlorhydrique N jusqu'à pH 7, puis 2 ml d'éthanol et 140 mg de bromure de *p*-phénylphénacyle. On porte à reflux pendant 90 min. Au refroidissement, une gomme jaune précipite. On extrait avec un mélange d'éther et de chloroforme; On dilue à l'éther, ce qui provoque la précipitation de cristaux, qui sont essorés et recristallisés dans le chlorure de méthylène et l'éther. C'est l'ester de méthyle et de *p*-phénylphénacyle (IV):

F = 140° (Kof.)
$C_{31}H_{36}O_6$ (504·65) Calc.%: C 73·73 H 7·19
Tr.: C 73·6 H 7·2 (Lyon)

Spectre U.V.: λ_{max} 285 mμ (ε = 24,800; MeOH).
Spectre I.R.: Fig. 1(b).

D.R.: Dispersion simple positive (effet Cotton inaccessible), $[\alpha]_{600}$ −13°, $[\alpha]_D$ −13°, $[\alpha]_{400}$ +32°, $[\alpha]_{270}$ +105°, $[\alpha]_{255}$ +139° (*c* = 2·7; MeOH) (Fig. 3).

Ozonisation de l'acide agathique (F. L.)

(a) *Obtention du dicéto-acide* (VI). On ozonise une solution de 2·42 g d'acide agathique dans 30 ml de chlorure de méthylène et 4 ml de pyridine, à −70°, jusqu'à coloration bleue. Après retour à la température ordinaire, on évapore le chlorure de méthylène, on dilue à l'eau, on acidifie par l'acide chlorhydrique concentré, et on extrait de la manière habituelle. On obtient ainsi 2 g d'une masse

[11] J. M. Conia et P. Leriverend, *C.R. Acad. Sci., Paris* **250**, 1078 (1960).

vitreuse jaune incristallisable. On chromatographie sur 110 g d'acide silicique (colonne préparée avec de l'éther de pétrole, produit mis en solution dans le minimum d'éther).

Le mélange éther de pétrole-éther (5:5) élue 97 mg de cristaux, F = 178°, ne présentant en I.R. ni les bandes du groupe C=CH_2, ni celle d'un carbonyle cétonique [ν(C=O) 1690 cm^{-1}; acide ($CHCl_3$)]. Il s'agit sans doute d'un peroxyde.[9]

Le mélange éther de pétrole-éther (4:6) élue 1·29 g de cristaux F = 80–130°, recristallisés dans l'acétone et l'hexane.

Il s'agit du dicéto-acide (VI), comme le montre sa dispersion rotatoire.

F = 138–139° (cap.)
$C_{17}H_{26}O_4$ (294·4) Calc. %: C 69·36 H 8·90
Tr.: C 69·1 H 8·4 (Lyon)

Spectre U.V.: λ_{max} 282 mμ (ε = 51; EtOH).
Spectre I.R.: ν(OH) 3300–2400 cm^{-1}, ν(C=O) 1710–1680 cm^{-1}, ν(C—O) 1260 cm^{-1} (KBr).
D.R.: Effet Cotton négatif $[\alpha]_{600}$ −20°, $[\alpha]_D$ −22°, $[\alpha]_{307\cdot5}$ −2397°, $[\alpha]_{275}$ +2528° (c = 0·22; EtOH).

(b) *Obtention du cétol* (VII). L'acide agathique est ozonisé comme précédemment, mais l'extrait éthéré contenant la fraction acide est lui-même extrait deux fois avec 50 ml de potasse à 10%. La fraction acide est ensuite isolée de la façon habituelle, et chromatographiée sur acide silicique. Le mélange éther de pétrole-éther (1:2) élue une fraction cristallisable dans l'acétone et l'hexane. [Les eaux-mères et les fractions non cristallisées de la chromatographie sont traitées, comme indiqué ci-dessous, pour obtenir la cétone α,β-éthylénique (VIII)]. Il s'agit sans doute du *cétol-acide* (VII), comme le montre notamment sa dispersion rotatoire. Il est aussi possible que ce produit soit un cétol ponté, analogue à ceux qu'ont décrit Johnson *et al.*[10]; l'analogie (antipodale) des dispersions rotatoires de ce produit et de la 5 α-hydroxy cholestane-3-one[11] nous fait plutôt pencher pour la structure indiquée.

F = 264° (Kof.)
$C_{17}H_{26}O_4$ (294·4) Calc. %: C 69·36 H 8·90
Tr.: C 69·5 H 8·6 (Lyon)

Spectre U.V.: inflexion à 280 mμ (ε = 32; EtOH)
Spectre I.R.: ν(OH) 3300 cm^{-1} ν(C=O) 1725 cm^{-1} ν(CO_2H) 1715 cm^{-1} (KBr).
D.R.: Effet Cotton positif $[\alpha]_D$ +30°, $[\alpha]_{600}$ +196°, $[\alpha]_{307\cdot5}$ +1517, $[\alpha]_{290}$ −153°, (c = 0·2; MeOH)

Formation de la cétone éthylénique-acide (VIII) (F. L.)

On dissout 1·2 g du dicéto-acide (VI) dans 60 ml de méthanol contenant 550 mg de méthylate de sodium. On porte à reflux pendant 20 hr. Après refroidissement, on acidifie à l'acide chlorhydrique, on évapore une partie du méthanol sous vide, on dilue à l'eau et on extrait de la manière habituelle. On obtient 984 mg d'une masse jaune semi-cristalline, qui est chromatographiée sur 60 g d'acide silicique (colonne préparée à l'éther de pétrole). Le mélange éther de pétrole-éther 45:55 élue 763 mg de cristaux F = 189–190°, qu'on recristallise dans l'acétone et l'hexane. On obtient ainsi la cétone éthylénique-acide (VIII):

F = 190–191° (Kof.)
$C_{17}H_{24}O_3$ (276·4) Calc. %: C 73·88 H 8·75
Tr.: C 73·8 H 8·7 (Lyon)

Spectre U.V.: λ_{max} 243 mμ (ε = 15400).
Spectre I.R.: ν(COOH) 1720 cm^{-1} ν(C=O) 1650 cm^{-1} ν(C=C) 1625 cm^{-1} (KBr).
D.R.: Effet Cotton négatif $[\alpha]_{600}$ +8°, $[\alpha]_D$ +8°, $[\alpha]_{350}$ −72°, $[\alpha]_{342\cdot5}$ −1147°, $[\alpha]_{300}$ +4250°, $[\alpha]_{290}$ +5080° (c = 0·16; MeOH).

Par action du diazométhane sur ce produit, on obtient l'ester méthylique, F = 118° (XI), identique à celui dont la préparation est décrite plus bas.

[9] W. S. Johnson, J. J. Korst, R. A. Clement et J. Dutta, *J. Amer. Chem. Soc.* **82**, 614 (1960).
[10] W. Klyne, communication personnelle.

Ozonisation de la cétone éthylénique-acide (VIII) (F. L.)

On ozonise 400 mg du produit (VIII), F = 190°, dissous dans 25 ml de chlorure de méthylène et 3 ml de pyridine, à −70°. Le même traitment à l'eau oxygénée que pour l'ozonisation de l'acide daniellique, et l'isolement habituel, donnent 390 mg d'une masse vitreuse jaunâtre, chromatographiée sur 24 g d'acide silicique (colonne préparée à l'éther de pétrole, produit mis en solution dans le minimum d'éther). Les mélanges éther de pétrole-éther 45:55 puis 40:60 éluent 254 mg de cristaux, F = 186–188°, recristallisés dans le chloroforme et l'hexane. On obtient ainsi le diacide-cétone (IX):

F = 191° (Kof.)
$C_{16}H_{24}O_5$ (296·35) Calc.%: C 64·84 H 8·16
Tr.: C 64·28 H 7·97 (Lyon)

Spectre U.V.: λ_{max} 283 mμ (ε = 30; EtOH).
Spectre I.R.: Fig. 1(a).
D.R.: Effet Cotton négatif $[\alpha]_{600}$ −17°, $[\alpha]_D$ −16°, $[\alpha]_{400}$ −125°, $[\alpha]_{307\cdot5}$ −1830°, $[\alpha]_{270}$ +2550°, $[\alpha]_{260}$ +2415° (*c* = 0·2; MeOH) (Fig. 3a).

Le mélange de parties égales de ce produit et de son antipode (II), dissous dans le chloroforme et évaporé, fond à 190°.

Préparation du cétol-ester (X) (F. L.)

On ozonise comme précédemment 1 g d'acide agathique. Le produit brut est estérifié directement au diazométhane. Le solide brun obtenu (807 mg) est chromatographié sur 48 g d'alumine. Le benzène, puis les mélanges benzène-éther 3:1 et 1:1 éluent 270 mg de fractions incristallisables dont un traitement ultérieur en milieu alcalin montre qu'il s'agit d'un mélange de cétol et de cétone α,β-éthylénique. Le mélange benzène-éther 1:3 élue ensuite 452 mg de cristaux F = 229–232° (Kof.). Par recristallisation dans l'acétone et l'hexane, on obtient pur le cétol-ester (X). Ce corps a été décrit par Ruzicka, Bernold et Tallichet[9] comme étant le dicéto-ester isomère (VI) (CO_2Me au lieu de CO_2H), ce qui exclut sa dispersion rotatoire.

F = 232° (Kof.) 212–213°, déc. (cap.) [Litt. F = 217–219° ou 211–213°[9]]
$C_{18}H_{28}O_4$ (308·4) Calc.%: C 70·10 H 9·15
Tr.: C 69·9 H 9·10 (Lyon)

Spectre U.V.: λ_{max} 281 mμ (ε = 24; MeOH).
Spectre I.R.: ν(OH) 3400 cm^{-1} ν(C=O) ester 1710 cm^{-1} ν(C=O) cétone 1703 cm^{-1} ($CHCl_3$).
D.R.: $[\alpha]_{600}$ +59°, $[\alpha]_D$ +71°, $[\alpha]_{500}$ +109°, $[\alpha]_{307\cdot5}$ +1394°, $[\alpha]_{290}$ +32°, $[\alpha]_{270}$ −129° (*c* = 0·2; EtOH) [Litt. $[\alpha]_D$ +70·7°[9]].

Déshydratation du cétol-ester (X) *en cétone éthylénique-ester* (XI)

La déshydratation se fait à reflux dans une solution 0·1 N de méthylate de sodium dans le méthanol, selon Ruzicka *et al.*[9]

F = 118° [Litt. 116–117°[9]]

Spectre U.V.: λ_{max} 242 mμ (ε = 15800; EtOH).
Spectre I.R.: ν(C=O) ester 1710 cm^{-1} ν(C=O) cétone 1675 cm^{-1} ν(C=C) 1620 cm^{-1} ($CHCl_3$).
D.R.: Effet Cotton négatif complexe $[\alpha]_{600}$ +42°, $[\alpha]_D$ +39°, $[\alpha]_{400}$ −18°, $[\alpha]_{350}$ −828°, $[\alpha]_{347\cdot5}$ −794°, $[\alpha]_{340}$ −850°, $[\alpha]_{290}$ +4640° (*c* = 0·15; EtOH) [Litt. $[\alpha]_D$ = 48·7°[9]].

Ozonisation de la cétone éthylénique-ester (11) *et formation de l'ester de méthyle et de* p-*phénylphénacyle* (XIII) (F. L.)

On ozonise 303 mg de la cétone éthylénique-ester (XI) dans 25 ml de chlorure de méthylène et 2 ml de pyridine, à −70°. A température ordinaire, on ajoute ensuite 5 ml d'eau oxygénée à 30% et 5 ml de potasse aqueuse à 10%, avec agitation. Après 17 hr de repos, on dilue à l'eau, évapore le chlorure de méthylène à froid sous vide. La fraction acide est extraite à l'éther de la manière habituelle. On obtient 274 mg de solide jaunâtre incristallisable même après chromatographie sur Florisil et sur acide silicique.

Le mode opératoire d'ozonisation de Turner[14] donne le même résultat. Le diester méthylique, obtenu par le diazo-méthane, ne cristallise pas plus que les sels de diéthylamine ou de S-benzylisothiouronium. Finalement, on forme l'ester de *p*-phénylphénacyle, par la technique décrite plus haut pour la préparation de l'antipode (IV).

Le produit, (XIII), est recristallisé dans le chlorure de méthylène et l'éther, ou l'éthanol:

F = 141° (Kof.)
$C_{31}H_{36}O_8$ (504,65) Calc.%: C 73·79 H 7·19
Tr.: C 73·9 H 7·3

Spectre U.V.: λ_{max} 284 mμ (ε = 25,500; MeOH).

Spectre I.R.: ν(C=O) ester de phénacyle 1735 cm^{-1} ν(C=O) ester 1720 cm^{-1} ν(C=O) cétone 1710 cm^{-1} ($CHCl_3$) (Fig. 1b).

D.R.: Dispersion simple négative (Effet Cotton inaccessible) $[\alpha]_{600}$ +17°, $[\alpha]_D$ − 0°, $[\alpha]_{400}$ −34°, $[\alpha]_{370}$ −76°, $[\alpha]_{320}$ −153° (*c* = 0·28; MeOH) (Fig. 3).

Nous remercions Mlles L. Ohnimus et H. Herrmann, qui ont effectué la plupart des déterminations spectrophotométriques et spectropolarimétriques, et Mlle J. Boissier et M. Hoffer, qui ont pris les clichés de poudre.

L'oléorésine de *Daniellia oliveri* nous a été fournie par la Direction des Eaux, Forêts et Chasses de l'Oubangui-Chari, que nous remercions très sincèrement

[14] R. B. Turner, *J. Amer. Chem. Soc.* **72**, 582 (1950).

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SOME KETOMANOYL OXIDES

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Abstract—1-Keto and 3-ketodihydromanoyl oxides have been prepared and their rotatory dispersion curves compared with that of 2-ketodihydromanoyl oxide.

IN view of the strong positive Cotton effect exhibited by 2-ketomanoyl oxide,[1] it was thought desirable to prepare the corresponding 1- and 3-ketones.

Accordingly, 8α,13-oxidolabdan-2-one[2] (2-ketodihydromanoyl oxide) (I) was reduced with sodium borohydride to an alcohol identical with that obtained by Grant[3] and considered to be the β-epimer. This reacted with phosphorus pentachloride giving a mixture of the olefin II and the chloro-compound III which could be dehydrochlorinated to II. When phosphorus oxychloride in pyridine was used for the dehydration, II was the sole product. Epoxidation of II, followed by reduction of the product with lithium aluminium hydride yielded an alcohol which was not characterized, but oxidized to the ketone IV.

I

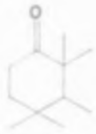
II

III

IV

V

VI



VII

That this was, in fact, 8α,13-oxidolabdan-3-one was demonstrated, first by hydrogenation of II to 8α,13-oxidolabdane to show that no skeletal changes had taken place; and second by the usual retropinacol ring contraction on the 3β-alcohol, by which V was obtained as an oil. Ozonolysis of this gave acetone, isolated as its 2,4-dinitrophenylhydrazone in high yield, together with a substance having I.R. absorption at 1746 cm^{-1} characteristic of a cyclopentanone.

The preparation of the 1-ketone was accomplished by oxidation of II with selenium dioxide in acetic acid. The resulting crude allylic acetate was hydrolysed, then

[1] P. K. Grant and R. Hodges, *Chem. & Ind.* 1300 (1960).
[2] Prepared by hydrogenation of 2-ketomanoyl oxide extracted from the wood oil of Dacrydium Colensoi, and generously supplied by Dr. P. K. Grant.
[3] P. K. Grant, *J. Chem. Soc.* 860 (1959).

oxidized to the en-one VI. This had U.V. absorption (in methanol) at 225 mμ, ε 8400, consistent with its structure. On hydrogenation it yielded 8α,13-oxidolabdan-1-one (VII). In order to confirm its structure this was reduced by the Wolff-Kishner procedure to 8α,13-oxidolabdane. These experiments support the placing of the carbonyl group in natural ketomanoyl oxide at C_2 making it the only diterpene known to be oxygenated at this position.

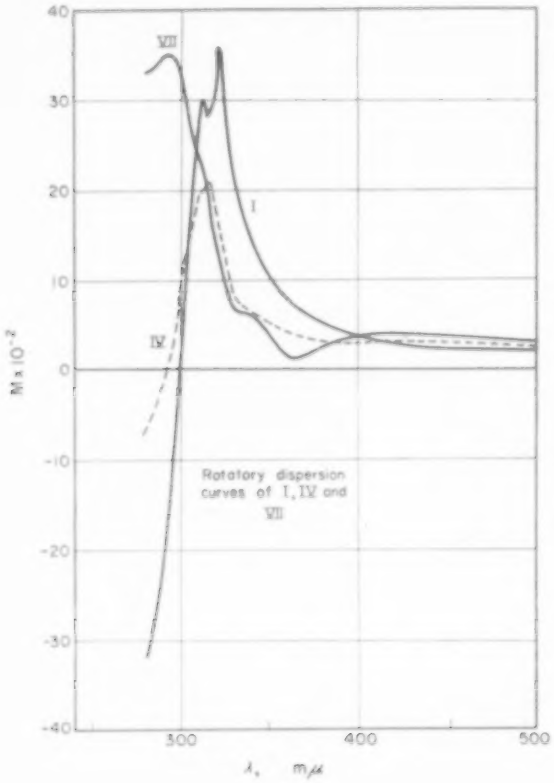


FIG. 1.

The frequency of the carbonyl I.R. absorption bands of the 1-, 2- and 3-ketones are in the expected order at 1706·5, 1711·5 and 1708 cm^{-1} (in CCl_4) though that of the 2-ketone is appreciably lower than is normal for a cyclohexanone with no α-substituents. This might conceivably be caused by the strain which must be introduced into ring A by the four axial substituents at C_4, C_8, C_{10} and C_{13}.

The rotatory dispersion curves of I, IV and VII are similar to those of their steroid analogues, though it might be expected that the methyl substituents at C_4 would cause a considerable difference in I and IV. The curve of IV is also similar to those of 8β-methyl triterpenes, e.g. dipterocarpol and onocerone dione-I, which are thought[4] to exist largely in the true A-boat form in solution. Hence IV, which is even more congested on the β-face than dipterocarpol, probably has ring A in a boat form.

[4] R. Hanna, J. Levisalles and G. Ourisson, *Bull. Soc. Chim.* 1936 (1960).

However, a very high degree of compression would be needed for the A-boat form to be preferred in I, for in this case the additional unfavourable interaction between the 3β-hydrogen and the methyl group at C_{10} would be introduced.

The octant rule[5] would predict that if ring A assumes a chair form, I should exhibit a positive Cotton effect of low amplitude, since the nearest atoms to the carbonyl group to make any contribution should be C_8 and C_{11}. The nature of the Cotton effect of the A-boat conformation of I is hard to predict in view of the asymmetry introduced into ring A itself in this form. Until other 2-keto di- and triterpenes with varying amounts of 1,3-diaxial substitution are available for comparison, no reliable deductions regarding the shape of ring A in these compounds can be made.

EXPERIMENTAL

Rotations were measured in chloroform at room temperature unless otherwise stated. M.p.'s were taken on a Kofler block and are corrected. The alumina used for chromatography had activity II. Light petroleum refers to the fraction with b.p. 60–80°.

8α,13-*Oxido-labd*-2-*ene* (II). 8α,13-Oxidolabdan-2-one (260 mg, $[\alpha]_D$ +34° c, 1·1) was allowed to react with sodium borohydride (100 mg) in aqueous methanol (15 ml, 80%) for 2 hr. After crystallization from aqueous methanol the product (193 mg) had m.p. 81·5–83°, $[\alpha]_D$ +40° (*c*, 0·9). Dehydration of this alcohol using the conditions described by Grant gave 8α,13-oxidolabd-2-ene, m.p. 84–85°, $[\alpha]_D$ +37° (*c*, 1·0). When the dehydration was carried out by shaking the alcohol (305 mg) with phosphorus pentachloride (300 mg) in light petroleum (20 ml), the product was an oil consisting of a mixture of the choro-compound (III) and II, which could be isolated by repeated crystallization from methanol.

8α,13-*Oxidolabdan*-3-*one* (IV). II (125 mg) was allowed to react with a solution of monoperphthalic acid in ether (7 ml, 0·5 molar) for four days at 20°. The resulting oil was heated under reflux with lithium aluminium hydride (60 mg) in tetrahydrofuran (10 ml) for 10 hr. The product was adsorbed from benzene on alumina, eluted with ether, then oxidized in acetone with 8 N chromic acid/sulphuric acid. After dilution with water, ether extraction and chromatography on alumina, 8α,13-*oxidolabdan*-3-*one* formed needles (81 mg) from aqueous methanol, m.p. 70–71·5°, $[\alpha]_D$ +33° (*c*, 0·9). (Found: C, 78·45; H, 10·85. $C_{20}H_{34}O_2$ requires: C, 78·4; H, 11·2%).

Retropinacol rearrangement. IV (205 mg) was allowed to react with sodium borohydride (100 mg) in aqueous methanol (20 ml, 80%) for 1 hr. The product in light petroleum (15 ml) was shaken with phosphorus pentachloride (300 mg) for 10 min, then filtered through alumina. Evaporation gave an oil (V) which could not be crystallized and whose I.R. spectrum did not show absorption bands characteristic of an —OH group, a disubstituted double bond or a chloro-compound. Ozonolysis of V (184 mg) in acetic acid (18 ml) yielded acetone, isolated as its 2,4-dinitrophenylhydrazone (112 mg), together with a gum with I.R. absorption at 1746 cm^{-1} (in CCl_4).

8α,13-*Oxidolabd*-2-*en*-1-*one* (VI). II (85 mg) was heated under reflux with selenium dioxide (150 mg) in acetic acid (5 ml) for 15 min. The crude product which had I.R. absorption at 1726 cm^{-1}, was hydrolyzed by heating for 1 hr with sodium hydroxide (1 g) in aqueous methanol (10 ml, 80%). Chromatography on alumina afforded an alcohol which was not characterised but oxidised in acetone with 8 N chromic acid/sulphuric acid to VI. This crystallized as needles (51 mg) from methanol, m.p. 135–136°, $[\alpha]_D$ +86° (*c*, 0·8). (Found: C, 78·9; H, 10·6. $C_{20}H_{32}O_2$ requires C 78·6; H, 10·5%).

A similar selenium dioxide oxidation was carried out on the crude product (140 mg) from the reaction of phosphorus pentachloride with the 2-alcohol. After hydrolysis, two products were separated by chromatography; an alcohol (76 mg) as before, and 2-*chloro*-8α,13-*oxidolabdane* (III) which formed needles (29 mg) from methanol, m.p. 111–112°, $[\alpha]_D$ 0° (*c*, 0·6). (Found: C, 73·95; H, 10·85; Cl, 10·85. $C_{20}H_{35}OCl$ requires: C, 73·5; H, 10·8; Cl, 10·85%).

8α,13-*Oxidolabdan*-1-*one* (VII). Hydrogenation of VI (40 mg) in ethyl acetate using 10% palladium on charcoal catalyst gave VII (35 mg) as needles from aqueous methanol, m.p. 80–81°, $[\alpha]_D$ +75° (*c*, 1·1). (Found: C, 78·8; H, 11·2. $C_{20}H_{34}O_2$ requires: C, 78·4; H, 11·2%).

Dehydrochlorination of III. III (20 mg) was heated under reflux with sodium hydroxide (1 g) in

[5] C. Djerassi, *Optical Rotatory Dispersion* p. 178. McGraw-Hill, New York (1960).

diethylene glycol (5 ml) for 15 hr. Isolation in the usual manner afforded II (15 mg), m.p. 84–85° undepressed with an authentic specimen. Catalytic hydrogenation of II gave 8α,13-oxidolabdane, m.p. 19–21° $[\alpha]_D$ +12° (*c*, 0·8), identical with a specimen prepared by the usual Wolff-Kishner reduction of either VII or I.

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ARYL TELLURIUM TRIHALIDES—II

CONDENSATION REACTION WITH METHYLKETONES AND AROMATIC COMPOUNDS CONTAINING ELECTRON-REPELLING GROUPS

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Abstract—Aryl tellurium trichlorides and tribromides undergo condensation reactions with acetone, acetophenone, N-dimethylaniline and resorcinol, giving rise to aryl tellurium dihalides. Aryl tellurium triiodides are not reactive. The dihalides derived from N-dimethylaniline and resorcinol undergo ionic interchange reactions with halide ions. When treated with reducing agents the dihalides derived from N-dimethylaniline are reduced to the corresponding tellurides, while the other dihalides are cleaved to the diaryl-ditellurides.

IT is known that aromatic selenenyl halides and pseudo-halides react with methylketones and with aromatic compounds containing electron-repelling groups giving rise to selenides.[1] It has been shown that several aryl tellurium trichlorides (I: X = Cl)[2–6] and some tribromides (I: X = Br)[4] react similarly, producing with acetone, acetophenone, N-dimethylaniline and resorcinol, aryl acetonyl tellurium dihalides (III), aryl phenacyl tellurium dihalides (V), aryl-*p*-dimethylaminophenyl tellurium dihalides (VII) and aryl-2,4-dihydroxyphenyl-tellurium dihalides (IX) respectively.

Only one of the halogen atoms of the trihalides is replaceable by an organic group, since, with excess of reagents II, IV, VI or VIII only dihalides formulated below are obtained:

I II III

R=CH_3, C_2H_5 X=Cl

These condensation reactions take place less readily with the aryl tellurium tribromides, and in the case of the corresponding triiodides (I : X = I)[4] no tellurium diiodides are obtained.

The greater reactivity of the aryl trichlorides as compared with the corresponding tribromides and triiodides is probably due to a decrease in the electrophilic character

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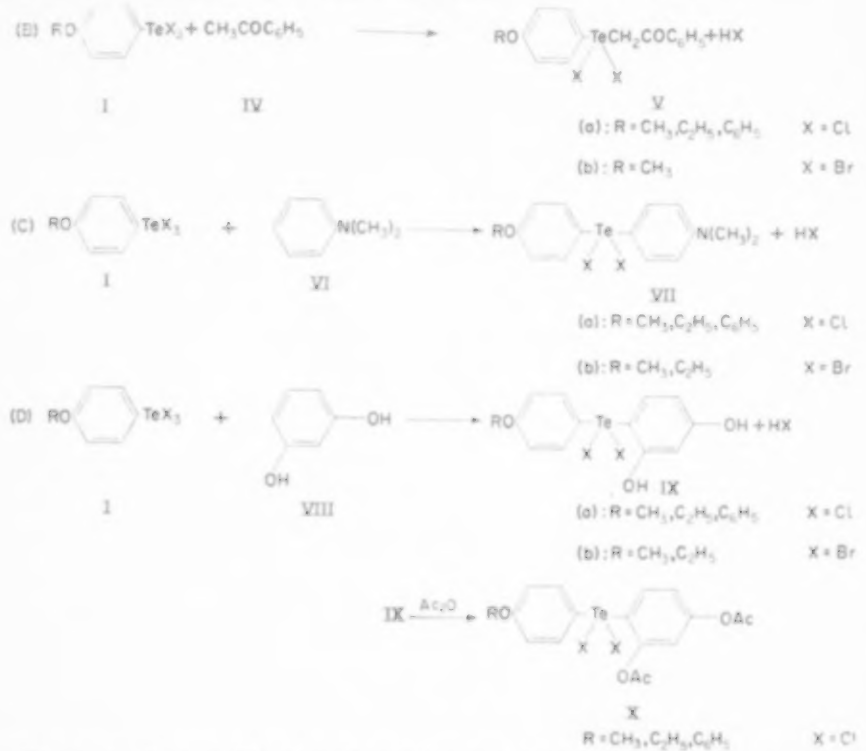
[1] H. Rheinboldt and M. Perrier, Bl. [5] **17**, 248, 249, 250, 251, 252, 759 (1950); **20**, 264, 379, 485–488 (1953), O. Behagel and Myller, *Ber. Dtsch. Chem. Ges.* **68**, 1549 (1935).
[2] G. T. Morgan and R. E. Kellett, *J. Chem. Soc.* 1080 (1926).
[3] L. Reichel and E. Kirschbaum, *Liebigs Ann.* **523**, 222 (1936).
[4] N. Petragnani, *Tetrahedron* **11**, 15 (1960).
[5] G. T. Morgan and H. D. K. Drew, *J. Chem. Soc.* 2307 (1925).
[6] H. O. K. Drew, *J. Chem. Soc.* 223 (1926).

of the positive fragment $(ArTeX_2)^+$, when bromine or iodine are substituted for chlorine. The reactivity of the aryl tellurium trihalides also decreases when the phenoxy group (I : R = C_6H_5) is substituted for the alcoxy group (I : R = CH_3 or C_2H_5). On the other hand, the aromatic reagents VI and VIII react readily and these reactions can be performed with aryl tellurium tribromides without difficulty, whereas the methylketones (II and IV), in the majority of the cases do not react with the tribromides under normal conditions and more drastic conditions lead to the formation of bromoacetone or phenacyl bromide and tarry products.

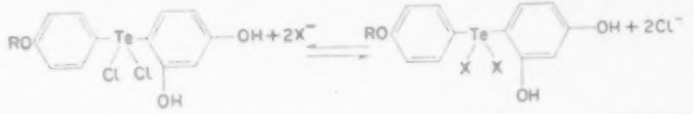
Studying the behaviour of the tellurium dihalides in water, it was found that VII and IX are stable, but III and V are hydrolysed to aryl tellurium oxohalides (XI)[3,7] and halogenoketone (XII). The formation of XII is not understood.


(B) RO TeX2 + CH3COC6H5
RO TeCH2COC6H5+HX
X X
I IV V
(a): R = CH3, C2H5, C6H5 X = Cl
(b): R = CH3 X = Br
(C) RO TeX3 + N(CH3)2
RO Te N(CH3)2 + HX
X X
I VI VII
(a): R = CH3, C2H5, C6H5 X = Cl
(b): R = CH3, C2H5 X = Br
(D) RO TeX3 + OH
RO Te OH + HX
X X
OH OH IX
I VIII
(a): R = CH3, C2H5, C6H5 X = Cl
(b): R = CH3, C2H5 X = Br
IX Ac2O RO Te OAc
X X
OAc
X
R = CH3, C2H5, C6H5 X = Cl

The aryl tellurium dihalides of type VII and IX (stable in water) undergo ionic interchange with other halide ions. When aryl-2,4-dihydroxyphenyl tellurium dichlorides (IX) are treated with excess of hydrobromic acid or concentrated aqueous solutions of potassium iodide, the corresponding dibromides and diiodides are obtained:

[7] N. Petragnani and G. Vicentini, Universidade São Paulo, Faculdade Filosofia, Ciências e Letras, Química No. 5 (1959).

Aryl-*p*-dimethylaminophenyl tellurium dichlorides (VII) react only with hydrobromic acid, forming the corresponding dibromides:



IX IX (X = Br, I)

In reduction of tellurium dichloride (III, V, VII, IX), for the purpose of obtaining tellurides, it was found that aryl acetonyl (III), aryl phenacyl (V), aryl-2,4-dihydroxyphenyl tellurium dichlorides (IX) undergo decomposition, forming diaryl ditellurides (XIII).[2–6,8] Only aryl *p*-dimethylaminophenyl tellurium (VII) are normally reduced to the corresponding aryl *p*-dimethylaminophenyl tellurides (XIV).

VII VII

The aryl *p*-dimethylaminophenyl tellurium diiodides (VII : X = I) may be prepared by the addition of iodine to the aryl *p*-dimethylaminophenyl telluride (XIV).

XIII

VII XIV (X = Cl, Br)

VII

EXPERIMENTAL

(A) *The Condensation of Trihalides with Acetone*

Acetonyl aryl tellurium dichlorides (III)

Acetonyl-(p-methoxyphenyl-) tellurium dichloride. *p*-Methoxyphenyl tellurium trichloride (0·34 g; 0·001 mole) was dissolved in acetone (5 cc) in a small glass capsule. The acetone was rapidly evaporated at room temp with evolution of hydrogen chloride leaving a white crystalline residue. This treatment was repeated 3–5 times and finally the residue was washed with a small volume of cold methanol. The dichloride (0·23 g; 65%) crystallized in colourless plates from benzene and pet ether (50–70°) m.p. 137–138°. (Found: Te, 35·15; Calc. for $C_{10}H_{12}O_2Cl_2Te$: Te, 35·28%).

[8] L. Reichel and E. Kirschbaum, *Ber. Dtsch. Chem. Ges.* **76**, 1105 (1943).

Acetonyl-(p-ethoxyphenyl-) tellurium dichloride similarly prepared (yield 75%) crystallized from benzene and pet ether (50–70°) in colourless needles, m.p. 134–135°. (Found: Te, 34·00; Calc. for $C_{12}H_{14}O_2Cl_2Te$: Te, 33·87%).

In the case of *p*-phenoxyphenyl tellurium trichloride a yellow-orange oil was obtained from which a small amount of the unaltered trichloride slowly crystallized.

The aryl tellurium tribromides and triiodides (I: R = CH_3, C_2H_5, C_6H_5) were recovered unchanged when treated rapidly at room temp with acetone. If the reaction mixture was heated or allowed to stand at room temp it gave rise to bromoacetone or iodoacetone (recognized by the irritating and tear-provoking character).

Hydrolysis. A small amount of acetonyl-(*p*-methoxyphenyl-) tellurium dichloride was treated with cold water. After an hour the white residue of *p*-methoxyphenyl-tellurium oxochloride was filtered and dried (m.p. 225–235°, with dec[7]). With boiling water the oxochloride separated immediately with the formation of chloroacetone recognized by its piquant smell and tear provoking character. The acetonyl-(*p*-ethoxy-phenyl-) tellurium dichloride suffers similar hydrolitic cleavage.

Reduction. Acetonyl-*p*-methoxyphenyl-) tellurium dichloride treated with excess of hydrated sodium sulphide at 95–100° formed di-*p*-methoxyphenyl ditelluride as a red oil which solidified when diluted with water. After recrystallization from pet ether (30–50°) red-green needles were obtained m.p. 59–60°.[2,3,5] Reduction with sodium bisulphite, zinc in chloroform or hydrazine sulphate also yielded the ditelluride. Similarly, from *p*-ethoxy-derivative the di-*p*-ethoxyphenyl ditelluride (m.p. 107°)[2,3,5] was obtained.

(B) *The Condensation of Trihalides with Acetophenone*

Phenacyl aryl tellurium dihalides (V)

Phenacyl-(p-methoxyphenyl-) tellurium dichloride. *p*-Methoxyphenyl tellurium trichloride (0·34 g; 0·001 mole) was intimately mixed with 0·36 g (0·003 mole) of acetophenone, hydrogen chloride evolution being observed and separation, after 24–48 hr, of the dichloride. This was isolated by dissolving the excess of acetophenone in ether, and washing rapidly with a small quantity of cold methanol. Weight: 0·25 g (yield 60%). Colourless brilliant prism were obtained from benzene and pet ether (50–70°), m.p. 136–137° (Found: Te, 30·24; Calc. for $C_{15}H_{14}O_2Cl_2Te$: Te, 30·04%).

Similarly the following compounds were prepared:

Phenacyl-(p-ethoxyphenyl-) tellurium dichloride (yield: 57%), crystallized from benzene and pet ether (50–70°) in colourless needles, m.p. 141–142° (Found: Te, 29·26; Calc. for $C_{16}H_{16}O_2Cl_2Te$: Te, 29·08%).

Phenacyl-(p-phenoxyphenyl-) tellurium dichloride (yield: 45·5%), crystallized from benzene and pet ether (50–70°) in colourless needles, m.p. 146–147° (Found: Te, 26·38; Calc. for $C_{20}H_{16}O_2Cl_2Te$: Te, 26·21%).

Phenacyl-(p-methoxyphenyl-) tellurium dibromide (yield: 29·2%), crystallized from benzene and pet ether (50–70°) in pale yellow needles, m.p. 151–152° (with dec). (Found: Te, 24·95; Calc. for $C_{15}H_{14}O_2Cl_2Te$: Te, 24·84%).

p-Ethoxyphenyl tellurium tribromide, *p*-phenoxyphenyl tellurium tribromide and the aryl tellurium triiodides (I: R = CH_3, C_2H_5, C_6H_5) do not react with acetophenone.

Hydrolysis. Phenacyl-(*p*-methoxyphenyl-) tellurium dichloride after several hours treatment with cold water was recovered unchanged. With boiling water, after few minutes *p*-methoxyphenyl tellurium oxochloride (m.p. 225–235, with dec[7]) and phenacylchloride (recognized by its irritating smell) were formed. The other dihalides react similarly with boiling water.

Reduction. Di-*p*-methoxyphenyl ditelluride is formed by reduction of *p*-phenacyl-*p*-(methoxyphenyl-) tellurium dichloride with excess of sodium sulphide at 95–100°, or sodium bisulphite, zinc in chloroform, hydrazine sulphate. Crystallized from pet ether (30–50°) in red-green needles, m.p. 50–60°.[2,3,5]

Similarly di-*p*-ethoxyphenyl ditelluride (m.p. 107°)[2,3,5] and di-*p*-phenoxyphenyl ditelluride (m.p. 88–88·5°)[6,7] may be prepared from the corresponding dihalides.

(C) *The Condensation of Trihalides with* N-*Dimethylaniline*

p-*Dimethylaminophenyl aryl tellurium dihalides* (VII)

p-*Dimethylaminophenyl-*(p-*methoxyphenyl-*) *tellurium dichloride.* *p*-Methoxyphenyl tellurium trichloride (0·34 g; 0·001 mole) was intimately mixed with 0·36 g (0·003 mole) N-dimethylaniline

noting evolution of heat and a transient bluish-green colour. After 24 hr the mixture was extracted several times with methanol leaving a yellow crystalline residue of the dichloride, 0·32 g (yield: 75%). The compound crystallized from methanol or benzene and methanol in yellow prisms, m.p. 170–172° (with dec). (Found: Te, 29·99; Calc. for $C_{15}H_{17}OCl_2N$ Te: Te, 29·96%).

p-*Dimethylaminophenyl-*(p-*ethoxypheny-*) *tellurium dichloride*. (yield 59·1%) similarly prepared crystallized from methanol in yellow needles, m.p. 153–154° (with dec). (Found: Te, 29·28; Calc. for $C_{16}H_{19}OCl_2N$ Te: Te, 29·01%).

p-*Dimethylaminophenyl-*(p-*methoxyphenyl-*) *tellurium dibromide* (yield 50·6%) similarly prepared crystallized from benzene and methanol in yellow-orange prisms, m.p. 183–184° (with dec). (Found: Te, 24·81; Calc. for $C_{15}H_{17}OBr_2N$ Te: Te, 24·79%).

p-*Dimethylaminophenyl-*(p-*ethoxyphenyl-*) *tellurium dibromide* 0·48 g (0·001 mole) *p*-ethoxyphenyl tellurium tribromide was mixed with 0·36 g (0·003 mole) N-dimethylaniline noting the appearance of a transient bluish-green colour. After 24 hr the mixture was extracted with warm benzene and the extract treated with pet ether, and slowly evaporated in the open air. The dibromide crystallized in orange needles, 0·26 g (yield: 49%) m.p. 121–123° (with dec). (Found: Te, 24·27; Calc. for $C_{16}H_{19}OBr_2N$ Te: Te, 24·13%).

p-*Dimethylaminophenyl-*(p-*phenoxyphenyl-*) *tellurium dichloride*. A solution of 0·40 g (0·001 mole) *p*-phenoxyphenyl tellurium trichloride and 0·36 g (0·001 mole) N-dimethylaniline in 15 cc benzene was allowed to stand for 24 hr at room temp. Concentration in vacuum caused the separation of the yellow crystalline dichloride, 0·20 g (yield: 41%). Crystallized from benzene and methanol in yellow needles, m.p. 194–195° (with dec). (Found: Te, 26·20; Calc. for $C_{20}H_{19}OCl_2N$ Te: Te, 26·15%).

p-*Dimethylaminophenyl-*(p-*phenoxyphenyl-*) *tellurium dibromide*. A solution of 0·55 g (0·001 mole) *p*-phenoxyphenyl tellurium tribromide and 0·36 g (0·003 mole) N-dimethylaniline in 15 cc benzene was allowed to stand for 24 hr at room temp. By concentrating in vacuum, the tribromide precipitated (m.p. 206–207°).[4] The filtrate treated with excess methanol precipitated a white flaky hydrolytic product of the tribromide. From the filtered solution a small amount of beautiful orange needles of the dibromide was obtained, m.p. 188–189° (with dec) (Analysis given below).

From mixtures of aryl tellurium triiodides (I: R = CH_3, C_2H_5, C_6H_5) and N-dimethylaniline (0·001 to 0·003 mole) treated in the same manner the starting triiodides were recovered. By heating the mixtures at 60° for 1 hr black oils were obtained.

Interchange reaction of p-*dimethylaminophenyl aryl tellurium dihalides*

p-Dimethylaminophenyl-(*p*-methoxyphenyl-) tellurium dichloride (0·42 g; 0·001 mole) was mixed in the cold with excess 40% hydrobromic acid. The mixture was diluted with water and dil ammonium hydroxide added dropwise. *p*-Dimethylaminophenyl-(*p*-methoxyphenyl-) tellurium dibromide separated as orange crystals (solution still being acid), 0·51 g (yield: 100%), m.p. 183–184° (with dec). A mixed m.p. with the dibromide obtained previously was not depressed.

Similarly, treating *p*-dimethylaminophenyl-(*p*-methoxyphenyl-) tellurium dibromide with excess of conc hydrochloric acid the corresponding dichloride was obtained. Similar reactions were performed with *p*-dimethylaminophenyl-(*p*-ethoxyphenyl-) tellurium dichloride and dibromide and in each case the yields were quantitative.

p-*Dimethylaminophenyl-*(p-*phenoxyphenyl-*) *tellurium dibromide*. *p*-Dimethylaminophenyl-(*p*-phenoxyphenyl-) tellurium dichloride (0·16 g; 0·00033 mole) was treated with 20 cc boiling 40% hydrobromic acid during 3 min. A yellow compound (the hydrobromide) was obtained and well dispersed in water. Ammonium hydroxide was added dropwise until the pale yellow hydrobromide was transformed in the orange dibromide. This was separated, washed with water and treated again with 10 cc boiling 40% hydrobromic acid for 1 min. The yellow hydrobromide was transformed again into the dibromide, as per the above manner. Weight: 0·19 g (Yield: quantitative). Crystallized from benzene and pet ether (50–70°) in orange needles, m.p. 188–189° (with dec). Mixed m.p. with the dibromide prepared by condensation reaction was not depressed). (Found: Te, 22·15; Calc. for $C_{20}H_{19}OBr_2N$ Te: Te 22·12%).

Similar reactions performed with the purpose of preparing the corresponding diiodides failed.

p-*Dimethylaminophenyl aryl tellurides*

p-*Dimethylaminophenyl-*(p-*methoxyphenyl-*)*telluride*. *p*-Dimethylamino-phenyl-(*p*-methoxyphenyl-) tellurium dichloride (0·42 g; 0·001 mole) was added to 3·6 g (0·015 mole) hydrated sodium

sulphide at 100° and the mixture maintained at this temp for 10 to 15 min. The telluride, a yellow orange oil, solidified after dilution of the mixture with water, 0·35 g (yield: 100%) and recrystallized from ethanol in colourless needles m.p. 96–97° (Found: Te, 36·04; Calc. for $C_{15}H_{17}ONTe$: Te, 35·96%).

By this same procedure the *p*-ethoxy- and *p*-phenoxy- derivatives were prepared:

p-*Dimethylaminophenyl*-(p-*ethoxyphenyl*-) *telluride*. (Yield: 100%) crystallized from ethanol in colourless needles, m.p. 126–127° (Found: Te, 34·59; Calc. for $C_{16}H_{19}ONTe$: Te, 34·59%).

p-*Dimethylaminophenyl*-(p-*phenoxyphenyl*-) *telluride*. (Yield: 100%) crystallized from ethanol in colourless needles, m.p. 75·5–76·5° (Found: Te, 30·58; Calc. for $C_{20}H_{19}ONTe$: Te, 30·60%).

The dibromides may similarly be reduced to the tellurides.

The tellurides treated in carbon tetrachloride solution with the equimolar amount of sulphuryl chloride or bromide gave rise respectively to the dichlorides and dibromides (mixed m.p. with the dihalides prepared by the condensation reactions were not depressed).

p-*Dimethylaminophenyl aryl tellurium diiodides*

p-*Dimethylaminophenyl*-(p-*methoxyphenyl*-) *tellurium diiodide*. To an ice-cooled solution of 0·35 g (0·001 mole) *p*-dimethylaminophenyl-(*p*-methoxyphenyl-) telluride was added, dropwise, a solution of an equimolar quantity of iodine in chloroform. Addition of pet ether (50–70°) precipitated the red diiodide, 0·60 g (yield: 100%). Crystallized from benzene and pet ether (50–70°) in dark red needles, m.p. 129–130° (with dec). (Found: Te, 21·02; Calc. for $C_{15}H_{17}OI_2NTe$: Te, 20·96%).

Similarly, the *p*-ethoxy- and *p*-phenoxy derivatives were prepared:

p-*Dimethylaminophenyl*-(p-*ethoxyphenyl*-) *tellurium diiodide*. (Yield: 100%), crystallized from benzene and pet ether (50–70°) in dark red needles, m.p. 96–97° (with dec). (Found: Te, 20·44; Calc. for $C_{16}H_{19}OI_2NTe$: Te, 20·50%).

p-*Dimethylaminophenyl*-(p-*phenoxyphenyl*-) *tellurium diiodide*. (Yield: 100%), crystallized from benzene and pet ether (50–70°) in dark red needles, m.p. 135–136° (with dec). (Found: Te, 18·97; Calc. for $C_{20}H_{19}OI_2NTe$: Te, 19·02%).

The *p*-dimethylaminophenyl aryl tellurium dihalides all melt with decomposition forming an intense blue liquid.

(D) *The Condensation of Trihalides with Resorcinol*

2,4-*Dihydroxyphenyl aryl tellurium dihalides* (IX)

2,4-*Dihydroxyphenyl*-(p-*methoxyphenyl*-) *tellurium dichloride*. A solution of 0·34 g (0·001 mole) *p*-methoxyphenyl-tellurium trichloride and 0·22 g (0·002 mole) resorcinol in a small volume methanol was allowed to stand overnight at room temp. Concentration of the solution to almost dryness yielded a colourless crystalline residue of the dichloride, 0·29 g (yield: 70%), crystallized from ether and pet ether (50–70°) in colourless plates, m.p. 182–183° (with dec). (Found: Te, 30·86; Calc. for $C_{13}H_{12}O_3Cl_2Te$: Te, 30·77%).

The *p*-ethoxy- and *p*-phenoxy- derivatives were prepared by the same method:

2,4-*Dihydroxyphenyl*-(p-*ethoxyphenyl*-) *tellurium dichloride*. (Yield: 70%), crystallized from ether and pet ether (50–70°) in colourless plates, m.p. 189–190° (with dec). (Found: Te, 29·72; Calc. for $C_{14}H_{14}O_3Cl_2Te$: Te, 29·76%).

2,4-*Dihydroxyphenyl*-(p-*phenoxyphenyl*-) *tellurium dichloride*. (Yield: 61%) crystallized from ether and pet ether (50–70°) in colourless plates, m.p. 181° (with dec). (Found: Te, 26·74; Calc. for $C_{18}H_{14}O_3Cl_2Te$: Te, 26·76%).

2,4-*Dihydroxyphenyl*-(p-*methoxyphenyl*-) *tellurium dibromide*. (Yield: 6%), crystallized from ether and pet ether (50–70°) in yellow needles, m.p. 179–180° (with dec). (Analysis given below).

2,4-*Dihydroxyphenyl*-(p-*ethoxyphenyl*-) *tellurium dibromide*. (Yield: 28%) crystallized from ether and pet ether (50–70°) in yellow plates, m.p. 190–191° (with dec). (Analysis given below).

p-Phenoxyphenyl tellurium tribromide did not react and was recovered unchanged.

Reduction: 2,4-Dihydroxyphenyl-(*p*-methoxyphenyl) tellurium dichloride treated with excess of hydrated sodium sulphide at 95–100°, or sodium bisulphite, zinc in chloroform, hydrazine sulphate formed di-*p*-methoxyphenyl ditelluride, crystallized from pet ether (30–50°) in red-green needles, m.p. 59–60°.[2,3,8]

Similarly di-*p*-ethoxyphenyl ditelluride (m.p. 107°)[2,5,8] and di-*p*-phenoxyphenyl ditelluride (m.p. 88–88·5°)[6,8] were obtained from the corresponding dihalides.

VOL. 12 1961

2,4-Dihydroxyphenyl aryl tellurium dibromides and diiodides from the corresponding dichlorides

2,4-*Dihydroxyphenyl*-(p-*methoxyphenyl*-) *tellurium dibromide*. A solution of 0·41 g (0·001 mole) 2,4-dihydroxyphenyl-(*p*-methoxyphenyl-) tellurium dichloride in a small volume of ethanol was treated with excess 40% hydrobromic acid. The yellow precipitate of the dibromide was separated by filtration, washed with dil hydrobromic acid and dried, 0·50 g (yield: 100%). Crystallized from ether and pet ether (50–70°) in yellow needles, m.p. 179–180° (with dec). Mixed m.p. with the dibromide prepared by condensation reaction was not depressed. (Found: Te, 25·30; Calc. for $C_{13}H_{12}O_3Br_2$ Te: Te, 25·33%).

2,4-*Dihydroxyphenyl*-(p-*methoxyphenyl*-) *tellurium diiodide*. This was similarly prepared by adding an excess of aqueous potassium iodide to an ethanolic solution of the dichloride maintaining the temp at 0–5°. It separated as a red paste which solidified after standing for 24 hr (yield: 100%). Crystallized from ether and pet ether (50–70°) in red prism, m.p. 130° (with dec). (Found: Te, 21·33; Calc. for $C_{13}H_{12}O_3I_2$ Te: Te, 21·35%).

Similarly the *p*-ethoxy- and *p*-phenoxy- derivatives were prepared:

2,4-*Dihydroxyphenyl*-(p-*ethoxyphenyl*-) *tellurium dibromide*. (Yield: 100%), crystallized from ether and pet ether (50–70°) in yellow plates, m.p. 190–191° (with dec). Mixed m.p. with the dibromide prepared by condensation reaction was not depressed (Found: Te, 24·61; Calc. for $C_{14}H_{14}O_3Br_2$ Te: Te, 24·65%).

2,4-*Dihydroxyphenyl*-(p-*ethoxyphenyl*-) *tellurium diiodide*. (Yield: 100%), crystallized from ether and pet ether (50–70°) in orange needles, m.p. 105° (with dec) or orange plates, m.p. 132° (with dec) or red prisms, m.p. 127° (with dec). (Found: Te, 20·80; Calc. for $C_{14}H_{14}O_3I_2$Te: Te, 20·86%).

2,4-*Dihydroxyphenyl*-(p-*phenoxyphenyl*-) *tellurium dibromide*. (Yield: 100%), crystallized from ether and pet ether (50–70°) in yellow prism, m.p. 181–182° (with dec). (Found: Te, 22·52; Calc. for $C_{18}H_{14}O_3Br_2$Te: Te, 22·56%).

2,4-*Dihydroxyphenyl*-(p-*phenoxyphenyl*-) *tellurium diiodide*. (Yield: 100%) crystallized from ether and pet ether (50–70°) in red needles, m.p. 122–124° (with dec). (Found: Te, 19·00: Calc. for $C_{18}H_{14}O_3I_2$ Te: Te, 19·34%).

2,4-Diacetoxyphenyl aryl tellurium dichlorides (X)

2,4-*Diacetoxyphenyl*-(p-*methoxyphenyl*-) *tellurium dichloride*. 2,4-Dihydroxyphenyl-(*p*-methoxyphenyl-) tellurium dichloride (0·21 g: 0·0005 mole) was treated with 5 cc acetic anhydride and a drop conc sulphuric acid, and allowed to stand for 24 hr at room temp. Water was then added, dropwise with stirring and cooling the mixture in an icebath. The dichloride separated as a solid (rapid addition of water caused the product to separate as an oil), 0·22 g (yield: 88%). Crystallized from benzene and pet ether (50–70°) in colourless prisms, m.p. 166–167°. (Found: Te, 25·61; Calc. for $C_{17}H_6O_5Cl_2$ Te: Te, 25·58%).

Similarly the *p*-ethoxy- and *p*-phenoxy- derivatives were prepared:

2,4-*Diacetoxyphenyl*-(p-*ethoxyphenyl*-) *tellurium dichloride*. (Yield: 88%), crystallized from denzene and pet ether (50–70°) in colourless needles, m.p. 162–168°. (Found: Te, 24·88; Calc. for $C_{19}H_{18}O_5Cl_2$ Te: Te, 24·89%).

2,4-*Diacetoxyphenyl*-(p-*phenoxyphenyl*-) *tellurium dichloride*. (Yield: 100%), crystallized from denzene and pet ether in colourless needles, m.p. 172–173°. (Found: Te, 22·33%; Calc. for $C_{22}H_{18}O_6$ Cl_2 Te: Te, 22·75%).

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SUGAR ESTERS—I

OXIDE FORMATION IN THE SYNTHESIS AND HYDROLYSIS OF SOME FLUORIDES AND PHOSPHATE ESTERS

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Abstract—Investigation of several routes to fluoro-carbohydrates and sugar phosphates has shown that appreciable formation of internal ethers may occur in certain cases.

RECENTLY the formation of anhydro sugars in the attempted synthesis of some sugar phosphates has been reported.[1] We have been interested in the synthesis both of sugar phosphates and fluoro-carbohydrates, and in both cases we have found that oxide formation may interfere with these syntheses. Furthermore we have encountered oxide formation in the hydrolysis of certain diaryl 2-hydroxyalkylphosphates: this type of compound usually hydrolyses with formation of cyclic esters.[2]

The following synthetic methods were amongst those examined in this work. *One*, the action of potassium fluoride upon sulphonyloxy derivatives.[3] *Two*, the action of potassium fluoride,[4] silver phosphate,[5] and silver diarylphosphates[6] upon halohydrins. *Three*, the action of acid fluorides, hydrogen fluoride[7a] and diaryl phosphoric acids[7b] upon epoxides.

6-Fluoro-6-deoxy hexoses have been prepared previously by direct replacement of

* Some of this work has been presented in part fulfilment of the requirements for the degree of M.Sc. Dublin University (1960).

[1] W. G. Overend and S. Brooks, *Chem. & Ind.* 471 (1960). We thank Professor Overend for the communication of some of his results to us prior to publication.

[2] E.g. *vide* P. E. Verkade, J. C. Stoppelenberg and W. D. Cohen, *Rec. Trav. Chim.* **59**, 886 (1940); D. M. Brown and A. R. Todd, *J. Chem. Soc.* 52 (1952); W. E. Cohn, *J. Amer. Chem. Soc.* **72**, 2811 (1950). H. S. Loring, L. W. Levy L. K. Moss and J. M. C. T. Ploesser, *Ibid.* **78**, 3724 (1956); D. M. Brown and H. F. Higson, *J. Chem. Soc.* 2034 (1957); D. M. Brown, R. Hall and H. F. Higson, *Ibid.* 1360 (1958).

[3] cf. eg. F. L. M. Pattinson and J. E. Millington, *Canad. J. Chem.* **34**, 757 (1956); E. D. Bergmann and I. Shahak, *Chem. & Ind.* 157 (1958).

[4] *Vide inter alia*, F. W. Hoffmann, *J. Org. Chem.* **75**, 425 (1950); *J. Amer. Chem. Soc.* **70**, 2596 (1948); G. Olah, *Acta. Chim. Acad. Sci. Hung.* **3**, 191 (1953); B. C. Saunders, *J. Chem. Soc.* 1773 (1948); E. D. Bergmann, *Ibid.* 3786 (1953); 3286 (1959).

[5] Eg. G. T. Cori, S. P. Colowick and C. F. Cori, *J. Biol. Chem.* **121**, 465 (1937); M. E. Krahl and C. F. Cori, *Biochemical Preparations* Vol. I, p. 33. John Wiley, New York (1949), S. P. Colowick, *J. Biol. Chem.* **124**, 557 (1938); W. R. Meagher and W. Z. Hassid, *J. Amer. Chem. Soc.* **68**, 2135 (1946); O. Reithel, *J. Amer. Chem. Soc.* **67**, 1056 (1945); M. Touster and A. R. Reynolds, *J. Biol. Chem.* **153**, 571 (1944); F. Lipmann and L. C. Tuttle, *Ibid.* **153**, 571 (1944).

[6] T. Posternak, *J. Amer. Chem. Soc.* **72**, 4824 (1950); *J. Biol. Chem.* **180**, 1269 (1949); O. Zervas, *Naturwiss.* **27**, 317 (1939); O. Reithel, *J. Amer. Chem. Soc.* **67**, 1056 (1945); G. M. Tener, R. S. Wright and H. G. Khorana, *J. Amer. Chem. Soc.* **78**, 506 (1956); R S. Wright and H. G. Khorana, *Ibid.* **77**, 3423 (1955); **78**, 811 (1956).

[7a] T. Knunyants, *Dokl. Akad. Nauk SSSR* **55**, 223 (1947); *Zh. Obshch. Khim.* **19**, 95 (1949). [7b] W. E. Harvey, A. M. Michalski and A. R. Todd, *J. Chem. Soc.* 2271 (1951). cf. G. P. Lampson and H. A. Lardy, *J. Biol. Chem.* **181**, 693 (1949).

terminal mesyloxy* residues[8] and since this work began Taylor *et al.*[9] have reported some similar experiments. The few recorded attempts to introduce secondary fluorine atoms by method *one* were unsuccessful.[10] As far as the authors are aware the action of potassium fluoride upon sugar halohydrins has not been examined, although silver fluoride has been used with varying success.[11] Silver diaryl phosphates have been reacted with sugar halides successfully on several occasions.[6] The action of diaryl phosphoric acids upon epoxides has also been described,[7b] but no investigation of the action of acid fluorides upon sugar epoxides has been reported.

Whilst we successfully synthesized several primary fluoro-sugars, including some previously known 6-deoxy-6-fluoro glucose[8] and galactose[9] derivatives, by method *one*, when we treated methyl-6-O-tosyl-α-D-glucoside with excess potassium fluoride in methanol we obtained material free from sulphur and fluorine; this was shown by its properties and by comparison with authentic material to be methyl-3,6-anhydro-α-D-glucoside (I). Likewise when methyl-2,3-di-O-mesyl-4,6-O-benzylidene-α-D-glucoside (II) was treated at 200° with potassium fluoride in ethylene glycol, some methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside (III) was obtained from the reaction mixture, together with unchanged starting material. In addition some loss of protecting groups occurred, as was indicated by the production of benzaldehyde and a little material which analysed correctly for a monofluoro methyl-α-D-hexoside. When potassium fluoride acted upon methyl-2,3-di-O-tosyl-4,6-O-benzylidene-α-D-glucoside (IV) and methyl-3-O-mesyl-4,6-O-benzylidene-α-D-glucoside (V) under similar conditions the epoxide (III) was in each case identified amongst the products. In contrast, the treatment of 1,2;5,6-di-O-isopropylidene-3-O-tosyl-D-glucofuranose with potassium fluoride, and of 1,2,3,6-tetra-O-acetyl-4-O-mesyl-β-D-glucose[13] with either potassium fluoride or sodium iodide under such severe conditions gave unsaturated materials, the structure of which will form the subject of a separate communication.

The replacement of other halogens by fluorine and by the diaryl phosphate group has been readily accomplished using the potassium[4] and silver[5,6] salts respectively. We have investigated the action of these reagents upon some sugar halohydrins. Whilst silver fluoride reacted anomalously with several primary halo-sugars,[14] we obtained a low yield of 1,2;3,4-di-O-isopropylidene-6-deoxy-6-fluoro-D-galactose (VI),[9] from the 6-deoxy-6-iodo derivative (VII),[15] by treatment with potassium fluoride. No action was observed when sodium fluoride was used. The solubility of the reagents in the solvent used may be a factor here.[16]

When, however, the following compounds were treated with potassium fluoride,

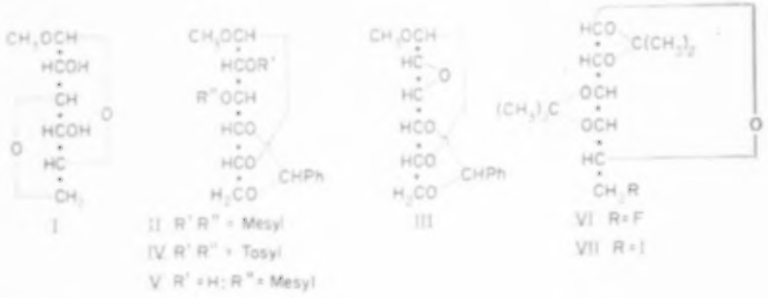
* Mesyl and tosyl are used here as abbreviations for methanesulphonyl and *p*-toluenesulphonyl respectively.

[8] B. Helferich and A. Gnütchel, *Ber. Dtsch. Chem. Ges.* **74**, 1035 (1941); B. Helferich and N. Vock, *Ibid.* **74**, 1807 (1941).
[9] N. F. Taylor and P. W. Kent, *J. Chem. Soc.* 872 (1958).
[10] B. Helferich and M. Vock *Ber. Dtsch. Chem. Ges.* **74**, 1807 (1941); F. H. Newth and L. F. Wiggins, *J. Chem. Soc.* 1734 (1950); P. W. Kent, O. Farmer and N. F. Taylor, *Proc. Chem. Soc.* 187 (1959).
[11] K. Brauns, *J. Amer. Chem. Soc.* **45**, 833 (1923); B. Helferich and E. Himmen, *Ber. Dtsch. Chem. Ges.* **61**, 1825 (1928); K. Hess, O. Littmann and R. Pfleger *Liebigs Ann.* **507**, 55 (1933); B. Helferich and R. Gootz, *Ber. Dtsch. Chem. Ges.* **62**, 2505 (1929);
[12] K. Freudenberg and B. Iver, *Ber. Dtsch. Chem. Ges.* **55**, 929 (1922).
[13] B. Helferich and A. Gnütchel, *Ber. Dtsch. Chem. Ges.* **74**, 1035 (1941).
[14] cf. B. Helferich and E. Himmen, *Ber. Dtsch. Chem. Ges.* **61**, 1825 (1928); K. Hess, O. Littmann and R. Pfleger, *Liebigs Ann.* **507**, 55 (1933).
[15] A. L. Raymond, *J. Amer. Chem. Soc.* **70**, 2785 (1948); K. Freudenberg, *Ber. Dtsch. Chem. Ges.* **59**, 100 (1926).
[16] cf. E. D. Bergmann and T. Blank, *J. Chem. Soc.* 3786 (1953).

oxides were obtained in every case. *trans*-2-Iodocyclohexanol (VIII), ethylene chlorhydrin (IX), 4-bromobutan-1-ol (X), methyl-6-deoxy-6-iodo-α-D-glucoside (XI), methyl-2-bromo-2-deoxy-4,6-O-benzylidene-α-D-altroside (XII), and methyl-3-bromo-3-deoxy-4,6-O-benzylidene-α-D-altroside (XIII), were treated in this manner, respectively giving, in varying yield, cyclohexeneoxide (XIV), ethylene oxide (XV), tetramethyleneoxide (XVI), methyl-3,6-anhydro-α-D-glucoside (I), methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside (III), and methyl-2,3-anhydro-4,6-O-benzylidene-α-D-mannoside (XVII).

Similarly silver diphenylphosphate rapidly reacted with the compounds (VIII), (X), and (XI). The corresponding oxides (XIV), (XVI) and (I) were identified amongst the products. Silver phosphate and silver dibenzyl phosphate both gave some methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside (III) when heated with compound (XII), whilst silver phosphate in boiling acetonitrile converted compound (XI) into the oxide (I).

Overend *et al.*[1] have shown recently that 3,6-anhydro sugars are produced by the action of silver diphenylphosphate upon some methyl-6-deoxy-6-iodo-glycosides. They further noted that acetylation of the free hydroxyl groups was sufficient to prevent reaction. We have confirmed these observations when attempting to prepare some phosphate esters by similar reactions. Thus silver iodide is rapidly set free in the reaction of methyl-6-deoxy-6-iodo-α-D-glucoside with silver phosphate, silver diphenyl

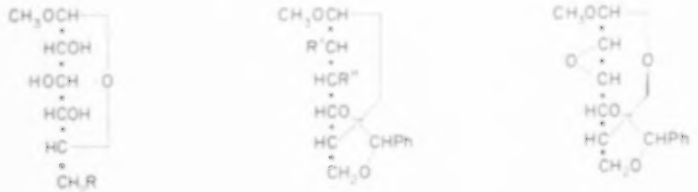


I

II R' R'' = Mesyl
IV R' R'' = Tosyl
V R' = H; R'' = Mesyl

III

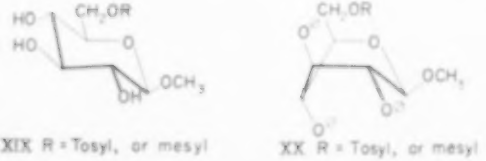
VI R = F
VII R = I



XI R = I

XII R' = Br; R'' = OH
XIII R' = OH; R'' = Br

XVII



XIX R = Tosyl, or mesyl or I

XX R = Tosyl, or mesyl or I

phosphate, or silver dibenzyl phosphate, but the only sugar derivative isolated was methyl-3,6-anhydro-α-D-glucoside (I).

The strong tendency for hydrogen-bond formation shown by fluoride ions[17a] (leading to the alkaline reaction of solutions of alkali metal fluorides) and the low nucleophilic character of these ions[17b] are probably important factors influencing the course of those reactions above which involve potassium fluoride. Both factors will favour competition by suitable ions when these are present in the media. Thus competition is considerable in alcoholic solvents, alkoxy ions giving ethers[18] and in the cases cited above the alkaline nature of the medium coupled with the suitable situation sterically of the hydroxyl group involved, favours ionization of and competition by this internal alkoxy group to the more or less complete exclusion of attack by the fluoride ion. Although initial formation of a fluoro compound followed by elimination of the elements of hydrogen fluoride is not excluded, and the literature reports concerning the stability of mono-fluoro compounds are conflicting,[19] we consider this unlikely, since a preliminary examination of some fluoro-sugars (e.g. methyl-6-deoxy-6-fluoro-D-galactosides) indicates that these require more severe conditions for conversion to anhydro sugars than the other halo sugars. The fluoro sugars are comparatively stable in the conditions of our experiments.

Further it is likely that formation of such a fluoro-compound would proceed with inversion. The *cis* fluorohydrins thus produced from the secondary halides would form epoxides only with difficulty. (cf. ref.[21])

The 1,2-*trans* arrangement of hydroxy and halo (or sulphonyloxy) groups is always favorable to epoxide formation,[20] and the *trans* diaxial arrangement found e.g. in compounds (XII) and (XIII) is particularly so.[21] Thus attempts to block the hydroxyl groups in these compounds by methylation resulted in dehydrobromination.[22]

We have attempted to prepare the *trans* fluorohydrins corresponding to compounds (XII) and (XIII) for a further investigation of this point, by the action of metal hydrogen fluorides, amine hydrogen fluorides, and hydrogen fluoride upon the epoxides (III) and (XVII). In one particular experiment hydrogen fluoride was reacted with methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside (III). Three fluorine containing fractions, and methyl-2,3-anhydro-α-D-alloside (XVIII) were among the products of this reaction but so far we have not proved conclusively the structure of any of our fluoro compounds.

The alkaline nature of the reagent is probably important in the action of potassium fluoride upon the 6-substituted methyl-glycosides. In neutral solution the stable conformation of these compounds will be as shown, (XIX),[23] and normal replacements

[17a] cf. P. H Groggins, *Unit Processes in Org. Synthesis* p. 182. McGraw-Hill, New York (1952); [b] cf. C. G. Swain and C. B. Scott, *J. Amer. Chem. Soc.* **73**, 141 (1953).

[18] cf. P. W. Kent, O. Farmer and N. F Taylor, *Proc. Chem. Soc.* 187 (1959).

[19] E.g. W. Hickinbottom, *Reactions of Organic Compounds* p. 525. Longmans, Green, London (1957); P. H. Groggins *Unit Processes in Organic Synthesis* p. 180. McGraw-Hill, New York (1952); A. L. Henne and J. B. Hinkamp, *J. Amer. Chem. Soc.* **67**, 1195 (1945); A. L. Henne, *Organic Reactions* **2**, 49 (1948); J. C. Bacon, C. W. Bradley, E. I. Hoegberg, P. Tarrant and J. T. Cassaday, *J. Amer. Chem. Soc.* **70**, 2653 (1948); F. W. Hoffmann, *J. Amer. Chem. Soc.* **70**, 2596 (1948); I. Knunyants, *Dokl. Akad. Nauk SSSR* **55**, 223 (1947).

[20] See for example, C. K. Ingold, *Structure and Mechanism in Organic Chemistry*. Cornell Univ. Press, New York (1953).

[21] E.g. D. H. R. Barton and R. C. Cookson, *Quart. Rev.* **10**, 67 (1956).

[22] cf. The ready methylation of methyl-3-bromo-3-deoxy-4-,6-O-benzylidene-α-D-glucoside, F. H. Newth, W. G. Overend and L. F. Wiggins, *J. Chem. Soc.* 10 (1947).

[23] C. Reeves, *J. Amer. Chem. Soc.* **72**, 1499 (1950); *Adv. in Carbohydrate Chem.* **6**, 108 (1951); J. T. Edwards *Chem. & Ind.* 1102 (1955).

occur[24] in neutral solution but in alkaline medium ionization of the hydroxyl groups is favoured, and this will tend to stabilize the form showing widest charge separation (*viz.* XX).[25]* Attack by fluoride ion is strongly hindered in this form; oxide formation is strongly favoured.

The results obtained with silver diphenyl phosphate again probably reflect the low nucleophilic character of the anion. Furthermore hydrolysis of phosphate triesters having a *vicinal* hydroxyl group in their structure usually involves cyclic esters rather than oxide formation,[2] which suggests that initial formation of a diphenyl phosphate, followed by oxide production, is unlikely, particularly since such a replacement would almost certainly give partial inversion; the resultant *cis* diol would be highly favourable to cyclic ester formation. Against this, formation of a cyclic ester from a diol having a fixed *trans* diaxial arrangement would be difficult. Some evidence for this was obtained in a preliminary examination of the dibenzyl phosphates produced by the action of dibenzyl phosphoric acid upon the epoxide (III),[26] when we noted the regeneration of some parent oxide upon alkaline treatment. Difficulties in purification of these dibenzyl phosphates have hindered a closer examination of the reaction, but support for the observation was given when a re-examination of the hydrolysis of dibenzyl *trans*-2-hydroxy-cyclohexyl phosphate[27] indicated that some cyclohexene oxide is formed. In this case the ring system is less rigid and cyclic ester formation consequently more facile.

In the case of the 6-iodo-6-deoxy glycosides there is little doubt that the C3 hydroxyl group plays an important part in directing the *initial* replacement reaction, since blocking this group by acetylation drastically lowers the rate. We consider it unlikely therefore that a phosphate ester forms initially in any of these reactions. The possibility remains that small amounts of silver oxide in the silver phosphate used may cause oxide formation, since it is known to do this; the amounts present, if any, would be insufficient to account for the observed yield however.

It is clear from these experiments that for replacements of this type, involving anions of low nucleophilic character, choice of solvents and reagents is critical if side reactions are to be avoided.

EXPERIMENTAL†

The experimental details given here concern the isolation of the oxide only in most cases. The identity of other products, isolated generally in modified conditions, will be dealt with elsewhere.‡ Yields of oxide are minimal in some cases owing to difficulties in isolation.

The Action of Potassium Fluoride upon Sulphonyloxy Derivatives

(1) *Methyl-6-O-tosyl-α-D-glucoside*[28]

(a) Methyl-6-O-tosyl-α-D-glucoside (0·05 g) and anhydrous potassium fluoride (3·0 g) in methanol (40 ml) were heated at 60° for 10 hr. The mixture was cooled and filtered and the filtrate evaporated

* N.B. Although XX is represented as fully ionized this is unlikely in the mild conditions used. With one of the three hydroxyls ionized, repulsions between this ion and the *p*-electrons of the remaining oxygens will partially stabilize the boat form here represented.

† M.p's. uncorrected.

‡ In preparation

[24] E.g. G. R. Barker and R. W. Goodrich, *J. Chem. Soc.* S 233 (1949); A. L. Raymond, and E. F. Schroeder, U.S. Pat, 2,365,776 (Dec. 26, 1944.); *Chem. Abstr.* **39**, 4434 (1944); *J. Amer. Chem. Soc.* **70**, 2785 (1948); A. B. Foster, W. G. Overend, M. Stacey and L. F. Wiggins, *J. Chem. Soc.*, 2542 (1949).

[25] cf. J. Speakman, *J. Chem. Soc.* 490 (1941), and refs. cited there; D. H. R. Barton, *Ibid.* 1197 (1945); D. H. R. Barton and R. C. Cookson, *Quart. Rev.* **10**, 62, 80 (1956).*

[26] A. R. Todd and D. M. Hayes, *J. Chem. Soc.* 2271 (1951).

[27] D. M. Brown, R. Hall and H. F. Higson, *J. Chem. Soc.* 1360 (1958).

[28] J. Compton, *J. Amer. Chem. Soc.* **60**, 395 (1938).

under reduced press to dryness. The white residue was extracted with boiling acetone and the extracts were cooled and filtered. The solvent was removed at the pump and the syrupy residue was examined by chromatography upon paper (Whatman No. 1) eluted with n-butanol–ethanol–water (4:1:5, v/v) and developed with aniline hydrogen chloride in methanol at 100° for 3 min. It gave two spots with R_F 0·51 and 0·56; Authentic methyl-3,6-anhydro-α-D-glucoside[19] (I) gave a spot R_F 0·56 in these conditions. Crystallization from hot anhydrous ethyl acetate gave material which did not reduce Fehling's solution but which readily did so after brief treatment with hot aqueous acid. Recrystallization from ethyl acetate gave material free from fluorine and sulphur as needles, m.p. 100–104°, raised on admixture with methyl-3,6-anhydro-α-D-glucoside.[19]

(b) The above reaction was repeated using ethylene glycol as solvent. The product, isolated in the usual manner, was a syrup, $[\alpha]_D^{17}$ +50° (*c*, 0·37 in H_2O), containing neither sulphur or fluorine. The syrup reduced Fehling's solution after acid treatment, and gave a single spot R_F 0·57, developing at room temp, when chromatographed on Whatman No. 1 paper (eluted with n-butanol–ethanol–water, 4:1:5, v/v) followed by spraying with alcoholic *p*-nitro-aniline hydrochloride.

(2) *Methyl*-2,3-*di*-O-*mesyl*-4,6-O-*benzylidene*-α-D-*glucoside*[20] (II)

Methyl-2,3-di-O-mesyl-4,6-O-benzylidene-α-D-glucoside (5 g) and anhydrous potassium fluoride (5 g) in ethylene glycol (50 ml) were heated under reflux at 140–150° for 1 hr, then at 195–200° for a further 15 min. The mixture was cooled and filtered. The filtrate ("A"), was poured into water (500 ml) and the aqueous mixture was extracted with chloroform. The combined chloroformic extracts were dried over sodium sulphate and evaporated to dryness at the pump. Fractional crystallization of the residue gave a solid (0·19 g) m.p. 190–195°, raised on recrystallization from chloroform–petroleum ether (60–80°) to 197–198°, depressed on admixture with compound (II), undepressed on admixture with authentic methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside (III),[21] $[\alpha]_D^{14}$ +130° (*c*, 0·1 in $CHCl_3$). [Found: C, 61·3; H, 5·92. Calc. for $2C_{14}H_{18}O_5{\cdot}H_2O$: C, 61·5; H, 6·27%]. The filtrate "A" was continuously extracted with ether for 36 hr, and the ether extract was evaporated to dryness and the residue recrystallized from ethanol to m.p. 179–180° (0·23 g). This compound contained fluorine,[22] was non-reducing, and had no aromatic peak in the ultra-violet absorption spectrum, and did not release benzaldehyde with hot aqueous acid; it did not contain sulphur, (Found: C, 36·4; H, 7·3; F, positive. $C_7H_{13}O_5F{\cdot}2H_2O$ requires: C, 36·2; H, 7·3%).

The residue separated from filtrate "A" was recrystallized from ethanol, giving prisms m.p. 188–189°, undepressed on admixture with authentic starting material, (2·96 g).

(3) *Methyl*-2,3-*di*-O-*tosyl*-4,6-O-*benzylidene*-α-D-*glucoside* (IV)

Methyl-2,3-di-O-tosyl-4,6-O-benzylidene-α-D-glucoside (0·97 g) was treated as above. The chloroform extract gave methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside, (III),[21] m.p. 187–189°, undepressed on admixture with authentic material, depressed on admixture with compound (IV) (0·008 g).

(4) *Methyl*-3-O-*mesyl*-4,6-O-*benzylidene*-α-D-*glucoside* (V)[20]

Methyl-3-O-mesyl-4,6-O-benzylidene-α-D-glucoside (0·7 g) was treated as above. Recrystallization of the chloroformic extract gave methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside, m.p. and m.p. mixed with an authentic sample, 197–198°, (0·09 g). This material showed absorption peaks in the infra-red at 745, 880, 895, 970, 978, 1012, 1046, 1073, 1150, and 1230 cm^{-1}.

The Action of Potassium Fluoride upon Halogen Compounds

(1) 1,2;3,4-*Di*-O-*isopropylidene*-6-*deoxy*-6-*iodo*-D-*galactose* (VI)

1,2;3,4-di-O-isopropylidene-6-deoxy-6-iodo-D-galactose (0·631 g) m.p. 67–69°, $[\alpha]_D^{18}$ −54·6° (*c*, 0·6239 in $CHCl_3$), in acetamide (5 ml) containing potassium fluoride (1·8 g) was heated under reflux for 96 hr. The cooled solution was poured into water (100 ml) and the aqueous mixture was extracted with chloroform (5 × 50 ml). The iodide present was determined, and corresponded to approximately 95% replacement. The chloroformic extract was dried and reduced to a syrup at the

[19] W. N. Haworth, L. N. Owen and F. Smith, *J. Chem. Soc.* 88 (1941).
[20] J. Honeyman, *J. Chem. Soc.* 3660 (1955).
[21] C. S. Richtmeyer and N. K. Hudson, *J. Amer. Chem. Soc.*, **63**, 1727 (1941).
[22] R. Belcher and T. S. West, *J. Chem. Soc.* 3577 (1959).

pump. Passage through a silica column gave an oil (0·1 g) which contained fluorine but not iodine, and which showed a strong peak in its infra-red absorption spectrum at 1050 cm^{-1} (C—F stretching?) with subsiduary peaks at 1010, 1027, 1110, and 1155 cm^{-1}, $n_{daylight}^{16}$ 1·4467, $[\alpha]_D^{12}$ −56° (*c*, 0·973 in $CHCl_3$). [Taylor *et al.*[9] record n_D^{20} 1·4475, $[\alpha]_D^{20}$ −51·4° (*c*, 1·284 in $CHCl_3$) for 1,2:3,4-di-O-isopropylidene-6-deoxy-6-fluoro-D-galactose].

(2) *trans-2-Iodocyclohexanol* (VIII)[35]

(a) This compound, (4·8 g, m.p. 38–40°), and potassium fluoride (8 g) in methanol (50 ml) were heated at 80° for 30 min. The mixture was cooled and filtered and methanol was removed from the filtrate at the pump. Petroleum ether was added (20 ml) and the mixture cooled at 5–10° for 3 hr. A small amount of *trans*-2-iodocyclohexanol (VIII) separated. The solution was filtered and petrol ether was removed from the filtrate at the pump leaving an oil which contained traces of iodine but no fluorine; A portion of this oil (1·5 g) was steam distilled and the oily distillate was refluxed with aqueous methanol (15 ml) containing three drops of conc hydrochloric acid for 15 min. Periodate titration of the resulting material[36a] indicated an approximate yield of cyclohexandiol of 15%. Thiosulphate titration[36b] of the oil indicated a slightly lower value for cyclohexene oxide (ca. 13%).

(3) *Ethylene chlorhydrin*

Commercial ethylene chlorhydrin (20 ml) and potassium fluoride (20 g) were warmed gently together under a current of nitrogen with vigorous stirring; A colourless gas was evolved which condensed in a receiver cooled to −15° to a colourless liquid which evaporated rapidly at approximately 10°. A solution of this gas in water containing a trace of hydrochloric acid was set aside for 48 hr. The solution was then treated with sodium periodate and the formaldehyde produced was removed in a stream of carbon dioxide and isolated as its dimedone derivative, m.p. 188–190°, (lit. m.p. 188–190°) and as its 2,4-dinitrophenylhydrazone m.p. 163–165° (lit. m.p. 168°).

(4) *4-Bromobutanol*

4-Bromobutanol (15 ml) and potassium fluoride (18 g) in ethylene glycol (30 ml) was heated to reflux, and a fraction boiling at 65–72°, which condensed as a colourless liquid with a characteristic odour, was distilled slowly from the mixture. This redistilled at 66–69°. This liquid showed peaks in the infra-red absorption spectrum at 915, 1030, 1070, 1175, and 1360 cm^{-1} identical with authentic tetrahydrofuran.

(5) *Methyl-2-bromo-2-deoxy-4,6-O-benzylidene-α-D-altroside*[37] (XII)

Methyl-2-bromo-2-deoxy-4,6-O-benzylidene-α-D-altroside,[37] (0·35 g) m.p. 116–118°, $[\alpha]_D^{16}$ +49° (*c*, 0·250 in $CHCl_3$) and anhydrous potassium fluoride (2 g) in dry methanol (70 ml) were heated under reflux for 10·5 hr. The cooled mixture was evaporated to dryness at the pump, and water (15 ml) was added to the residue. The aqueous mixture was extracted with chloroform (4 × 10 ml) and the extracts dried over sodium sulphate. The dried extracts were evaporated at the pump, and the white residue was recrystallized from chloroform–petroleum ether giving white feathery needles, m.p. 200°, $[\alpha]_D^{17}$ +127° (*c*, 0·2 in $CHCl_3$). This showed peaks in its infra-red absorption spectrum at 695, 705, 720, 745, 880, 899, 970, 978, 1012, 1046, 1073, and 1150 cm^{-1} (Found: C, 63·8; H, 6·27. Calc. for $C_{14}H_{16}O_5$; C, 63·6; H, 6·06%).

(6) *Methyl-3-bromo-3-deoxy-4,6-O-benzylidene-α-D-altroside* (XIII)[37]

Methyl-3-bromo-3-deoxy-4,6-O-benzylidene-α-D-altroside,[37] (0·083 g) m.p. 120–123°, $[\alpha]_D^{17}$ +127° (*c*, 0·49 in $CHCl_3$) in dry methanol (20 ml) containing potassium fluoride (1 g) was heated under reflux for 12 hr. The solvent was removed at the pump and the residue shaken with chloroform (8 ml) and

[35] G. J. Robertson and C. F. Griffith, *J. Chem. Soc.*, 1193 (1935); H. R. Bolliger and D. Prins, *Helv. Chim. Acta* **28**, 465 (1945).
[34] A. L. Raymond, *J. Amer. Chem. Soc.* **70**, 2785 (1948).
[35] W. J. Hickinbottom, *Reactions of Organic Compounds* p. 27. Longmans, Green, London (1948); L. Brunel, *Ann. Chim.* 1905, (vii), **6**, 219. (1905).
[36] [a] D. Gottlieb, C. G. Caldwell, and R. H. Hixon, *J. Amer. Chem. Soc.* **62**, 3342 (1940); N. F. Taylor, *Ibid.* **75**, 3912 (1953); R. L. Whistler and J. L. Hickson, *Ibid.* **76**, 1671 (1954).
[b] W. C. J. Ross, *J. Chem. Soc.* 2257 (1950).
[37] G. O. Richards and L. F. Wiggins, *J. Chem. Soc.* 2442 (1953).

water (20 ml). The chloroform layer was separated and the aqueous layer was re-extracted with chloroform (4 × 8 ml). The combined chloroformic extracts were dried over sodium sulphate and evaporated at the pump. The solid residue was recrystallized from chloroform–pet ether giving long colourless needles, m.p. 140–141°, raised on admixture with authentic methyl-2,3-anhydro-4,6-O-benzylidene-α-D-mannoside,[28] $[\alpha]_D$ +110° (*c*, 0·95 in $CHCl_3$). (Found: C, 62·3; H, 5·93. Calc. for $2C_{14}H_{16}O_5 \cdot H_2O$: C, 61·5; H, 6·27. Calc. for $C_{14}H_{16}O_5$: C, 63·6; H, 6·06%].

(7) *Methyl-6-deoxy-6-iodo-α-D-glucoside* (XI)[29]

Methyl-6-deoxy-6-iodo-α-D-glucoside,[29] m.p. 137–139°, (0·5 g) was heated under reflux in dry methanol containing anhydrous potassium fluoride (2 g) for 10 hr. The mixture was cooled and the solvent removed at the pump. The solid residue was extracted with several lots of boiling anhydrous acetone (5 × 10 ml). Examination of the combined extracts by paper chromatography upon Whatman No. 1 paper eluted with butan-1-ol–ethanol–water (4:1:5) indicated the presence of three compounds: (a) Starting material, R_F 0·14 (developed with methanolic aniline hydrogen chloride), (b) methyl-3,6-anhydro-α-D-glucoside (I), R_F 0·56 developed as (a) and (c), not identified, R_F 0·85, (fluoresced in ultra-violet light). The extracts were evaporated at the pump to a syrup from which methyl-3,6-anhydro-α-D-glucoside (I) was obtained with difficulty as cubes, m.p. 105–106°, undepressed on admixture with authentic material (0·016 g).

The Action of Silver Diphenyl Phosphate upon Halohydrins

(1) trans-2- *Iodocyclohexanol*

trans-2-Iodocyclohexanol (3·5 g) and silver diphenyl phosphate (4 g)[40] in methanol (40 ml) were refluxed for 1·5 hr. The cooled mixture was filtered and the filtrate was steam distilled rapidly. The first 50 ml of distillate was acidified with conc hydrochloric acid (4 drops) and refluxed for 1 hr. Titration with periodate[26a] indicated approx 20% conversion to the epoxide.

(2) 4-*Bromobutan*-1-ol

This compound (15 ml) was heated under reflux with silver diphenyl phosphate (4 g) in ethane diol and a fraction boiling at 60–70° was collected. This fraction was dried over sodium sulphate. Comparison of the infra-red absorption spectra of this compound and tetrahydrofuran confirmed its identity.

(3) *Methyl-6-deoxy-6-iodo-α-D-glucoside*

This compound (1·07 g) in toluene (15 ml) containing silver diphenyl phosphate (0·9 g) was heated under reflux in darkness for 24 hr. The solution was filtered and the filtrate was quickly washed with aqueous sodium hydrogen carbonate (10 ml) and water (15 ml), dried over sodium-sulphate and the solvent removed at the pump. The syrupy residue was examined by chromatography on Whatman No. 1 paper, eluted with butan-1-ol–ethanol–water (4:1:5), developed by spraying with methanolic aniline hydrogen chloride. Methyl-3,6-anhydro-α-D-glucoside (R_F 0·57) was present. The syrup gave a small amount of solid, m.p. 97–100°, on treatment with ethanol and ethyl acetate, recrystallized from ethyl acetate, m.p. 101–103°, raised on admixture with authentic methyl-3,6-anhydro-α-D-glucoside (I).

The Action of Silver Phosphate upon Halohydrins

(1) *Methyl-6-deoxy-6-iodo-α-D-glucoside* (XI)

This compound (0·3 g) and silver phosphate (0·25 g) in acetonitrile (5 ml) were heated under reflux for 6 hr. The cooled mixture was filtered and the filtrate was evaporated to dryness at the pump. The syrupy residue was dissolved in chloroform (10 ml) washed with water (5 ml), and dried over sodium sulphate and filtered through charcoal. The presence of methyl-3,6-anhydro-α-D-glucoside (I) was confirmed chromatographically as in the previous experiment. Attempts to crystallize the syrupy residue were unsuccessful, $[\alpha]_D^{16\cdot5}$ +45° (*c*, 0·66 in H_2O).

[28] G. J. Robertson and C. F. Griffith, *J. Chem. Soc.* 1193 (1935).
[29] M. Zief and R. C. Hockett, *J. Amer. Chem. Soc.* **67**, 1267 (1945); A. L. Raymond, U.S. Pat. 2,365,776 (Dec. 26, 1944). *Chem. Abstr.* **39**, 14434[5]
[40] T. Posternak, *J. Biol. Chem.* **180**, 1269 (1949).

(2) *Methyl-2-bromo-2-deoxy-4,6-O-benzylidene-α-D-altroside* (XII)

This compound (0·4 g) and silver phosphate (0·38 g) in acetonitrile (10 ml) were heated under reflux for 15 hr. The cooled solution was filtered and the solvent removed at the pump. The syrupy residue was dissolved in chloroform (25 ml) and the chloroform solution was washed with water (20 ml). The chloroform solution was dried and reduced to small volume (10 ml) at the pump. Petroleum ether (15 ml) was added and the mixture set aside at room temp for 24 hr. As no crystals separated the solution was allowed to evaporate slowly at room temp for several days. Methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside separated as long needles m.p. 190–192°, raised an admixture with authentic material, $[\alpha]_D$ +100° (*c*, 0·7 in $CHCl_3$), showing peaks in its infra-red absorption spectrum at 745, 880, 899, 970, 978, 1012, 1045, 1070, 1150, and 1230 $cm.^{-1}$

The action of silver dibenzyl phosphate upon methyl-2-bromo-2-deoxy-4,6-O-benzylidene-α-D-altroside (XII)

Methyl-2-bromo-2-deoxy-4,6-O-benzylidene-α-D-altroside (XII) (0·15 g) and silver diphenyl phosphate[41] (0·15 g) in benzene (5 ml) and toluene (5 ml) were heated under reflux for 6·3 hr. The solution was cooled and filtered, and the filtrate was washed with aqueous sodium hydrogen carbonate (10 ml) and water (5 ml), and the solvent was removed under reduced press. The syrupy residue was passed through a short charcoal column and a syrup was obtained which was induced to crystallize only with difficulty. Methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside (10 mg) was obtained as needles, m.p. 188–190°, undepressed on admixture with authentic material, $[\alpha]_D^{16}$ +125° (*c*, 0·04 in $CHCl_3$), infra-red spectrum identical.

The Alkaline Hydrolysis of Some Diaryl Hydroxyalkyl-Phosphates

(1) *Dibenzyl methyl-4,6-O-benzylidene-α-D-hexoside phosphate*[25]

Attempts to purify the dibenzyl phosphate produced by the method of Todd *et al.*[25] led always to partial decomposition of the ester. The following experiment was carried out using the crude syrupy ester, $[\alpha]_D^{16}$ +54° (Todd *et al.* report no constants.)[25]

The crude ester (1·3 g) in t-butanol (25 ml) containing sodium (0·8 g) was heated under reflux for 50 min. Carbon dioxide was passed through the cooled solution, and the solvent was removed at the pump. The semi solid residue was extracted with several lots of hot chloroform and the combined extracts were washed with water and dried over sodium sulphate. The solvent was removed at the pump and the syrupy residue was triturated with pet ether. The semi solid mass was crystallized from chloroform–pet ether, and after several recrystallizations crude methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside (III) was obtained (38 mg) m.p. 175–180°. Recrystallization from chloroform–benzene–petroleum ether gave needles, m.p. 185–187°, raised on admixture with authentic material, $[\alpha]_D^{17}$ +108° (*c*, 0·08 in $CHCl_3$).

(2) *Dibenzyl* trans-*2-hydroxycyclohexyl phosphate*[27]

This compound (m.p. 77–78°; 1·8 g) in t-butanol (20 ml) containing sodium (0·6 g) was heated under reflux for 0·5 hr. The solution was steam distilled and the first fraction of the distillate (50 ml) was collected. Ethanol was added to bring the volume up to 75 ml and aliquots of the solution were treated with dil sulphuric acid under reflux and then titrated with periodate.[26a] Separate aliquots were titrated with sodium thiosulphate.[26b] Cyclohexene oxide (4% ± 2%) was produced.

Attempted synthesis of some trans-*fluorohydrins from epoxides*

In a series of experiments potassium hydrogen fluoride, tributylamine di(hydrogen fluoride), and diisopropylamine hydrogen fluoride were heated under reflux with the oxides (III) and (XVII) in inert solvents. In most cases starting material was recovered unchanged.

Action of hydrogen fluoride upon methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside

In a further series of experiments hydrogen fluoride was reacted with (III). No appreciable reaction occurred below 40–50°.

[41] W. C. Lossen and A. Kohler, *Liebigs Ann.* **262**, 212 (1891).

Methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside (III) (1·2 g) in anhydrous acetylacetone (120 ml) containing 20 N hydrofluoric acid (3 ml) was kept at 40–50° for 5 days. Excess acid was then removed with calcium carbonate and the mixture was filtered. The residue was washed with acetone and the combined filtrate and washings were evaporated to dryness under reduced press. The syrupy residue was triturated with pet ether and the syrup which remained was passed through a column of silica gel. Successive elution with chloroform–pet ether (80–100°) (1:5, 2:5, 3:5) followed by chloroform–ethanol mixtures gave four main fractions.

Fraction one, colourless syrup, contained fluorine, showed peaks in the ultra-violet spectrum with λ_{max}^{EtOH} 2600 Å, and absorption peaks in the infra-red at 1050 (s), 835, 900, 1033, 1075, 1105, 1135, and 1190 cm^{-1} $[\alpha]_D^{17}$ +51° in ($CHCl_3$).

Fraction two, syrup, contained fluorine, showed absorption peaks at 2600 Å (ultra-violet) and 1055 (s), 895, 965, 1025, 1045, 1070, 1100, and 1133 cm^{-1} (infra-red), released benzaldehyde on treatment with dil aqueous acid, $[\alpha]_D^{17}$ +40° (in $CHCl_3$).

Fraction three, did not contain fluorine or release benzaldehyde on treatment with aqueous acid, showed no peak in the ultra-violet above 2200 Å, but showed peaks in the infra-red at 745, 835, 892, 905, 960, 980, 1075, and 1100 cm^{-1} with associated minor peaks at 715, 790, 1025, 1035, 1045, and 1055 cm^{-1}: m.p. 107–109°, $[\alpha]_D^{16}$ +151° in methanol. (Robertson[42] reports m.p. 105–107°, $[\alpha]_D^{15}$ +153° in methanol for methyl-2,3-anhydro-α-D-alloside.)

The identity of these fractions, and of some similar materials from the anhydro-mannoside, (XVII), are under investigation.

Acknowledgements—The authors wish to express their thanks to Professor Wesley Cocker for his interest in this work, and to Mr. E. R. Stuart for measurement of some infra-red spectra.

[42] G. J. Robertson, *J. Chem. Soc. Chem.* 472 (1938).

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SUBSTRATES FOR THE HISTOCHEMICAL LOCALIZATION OF SOME GLYCOSIDASES

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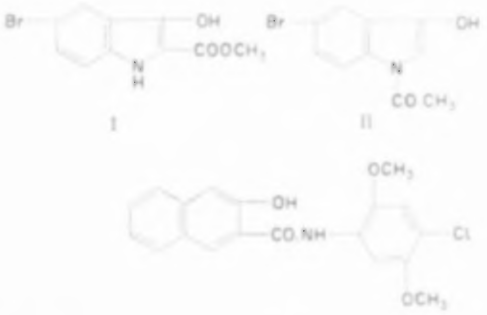
Abstract—Substrates for improved histochemical localizations of some glycosidases were required. The 2-acetamido-2-deoxy-β-D-glucoside, the β-D-glucoside, and the β-D-galactoside of 5-bromoindoxyl were synthesised through 1-acetyl-5-bromoindoxyl and the corresponding acetohalogenosugars. Attempts to prepare the β-D-glucuronide under a variety of conditions were unsuccessful, whereas acetobromo-methyl-glucuronate condensed with naphthoic-2-hydroxy-3-(2′:5′-dimethoxy-4′-chloro-anilide) and a potential histochemical substrate obtained: the preparation of the corresponding derivatives of β-D-galactose and 2-acetamido-2-deoxy-β-D-glucose are also described.

THE histochemical localization of the enzyme N-acetyl-β-glucosaminidase has been studied using the 2-acetamido-2-deoxy-β-D-glucoside of 1-naphthol as a substrate.[1] 5-Bromoindoxyl derivatives have been shown to have advantages in histochemical studies on esterases,[2] and it seemed likely that, provided the appropriate substrates could be prepared, the "indigogenic" principle[3] might be made the basis of improved localizations of glycosidases.



Indican (i.e. 3-β-glucosidoxyindole) has been synthesized[4] from acetobromoglucose through 1-acetyl-3-hydroxyindole or through methyl-3-hydroxyindole-2-carboxylate. Although preliminary experiments[5] indicated that the 2′-acetamido-2′-deoxy-β-D-glucoside could have been obtained through the corresponding indoxylate (I), the route through the 1-acetyl-3-hydroxy-5-bromoindole (II) was preferred since fewer stages were entailed. Acetochloroglucosamine[6] was condensed with the hydroxy

[1] D. Pugh and P. G. Walker, *4th Int. Congr. Biochem., Vienna p.* 45 (1958).
[2] S. J. Holt and R. F. J. Withers, *Proc. Roy. Soc.* B **148**, 520 (1958).
[3] R. J. Barnett and A. M. Seligman, *Science* **114**, 579 (1951).
[4] A. Robertson, *J. Chem. Soc.* 1937 (1927).
[5] F. B. Anderson and D. H. Leaback, unpublished results.
[6] D. H. Leaback and P. G. Walker, *J. Chem. Soc.* 4754 (1957).

compound (II) under conditions similar to those described previously[4] to give a 29 per cent yield of 1-acetyl-3-(2′-acetamido-3′:4′:6′-tri-O-acetyl-2′-deoxy-β-D-glucosidoxy)-5-bromoindole which was deacetylated with sodium methoxide to give the required 3-(2′-acetamido-2′-deoxy-β-D-glucosidoxy)-5-bromoindole. Under similar conditions the corresponding β-D-glucoside and β-D-galactoside were prepared from the respective acetobromosugars, but attempts to prepare the β-D-glucuronide from acetobromo-[7] or acetoiodo-methyl-glucuronate[8] under a variety of conditions were unsuccessful; no satisfactory explanation of this failure was obvious, but there have been other indications that acetohalogeno derivatives of glucuronic acid are atypical in their reactions. Attempts to prepare 3-β-D-glucuronidoxy-5-bromoindole by catalytic oxidation of the corresponding β-D-glucoside were also unsuccessful.[9]

The failure to prepare indoxyl β-glucuronides, and the advantages of having alternative histochemical substrates available, led to the synthesis of glycosides of other phenols which might give improved histochemical localizations. Phosphates of a series of complex phenols derived from 2-hydroxy-3-naphthoic acid (the Naphthol-AS phenols) have been shown to give good results as substrates for the localization of phosphatases.[10,11] Experiments[12] with several of the Naphthol-AS phenols showed that Naphthol AS-LC (III) [naphthoic-2-hydroxy-3-(2′:5′-dimethoxy-4′-chloro-anilide)] combined satisfactorily several properties which were desirable from histochemical considerations; the 2-acetamido-3:4:6-tri-O-acetyl-2-deoxy-β-D-glucoside of this phenol was prepared by a general method previously described,[6] and similar procedures yielded the 2:3:4:6-tetra-O-acetyl-β-D-galactoside and the 2:3:4-tri-O-acetyl-β-D-glucuronide methyl ester from the corresponding acetobromosugars. The 2-acetamido-2-deoxy-β-D-glucoside and the β-D-galactoside were obtained from the polyacetates by catalytic deacetylation from small volumes of methanol.[13] Of the several methods tried for the deacetylation and de-esterification of the 2:3:4-tri-O-acetyl-β-D-glucuronide methyl ester, a barium hydroxide method[14] was preferred.

The use of these compounds in the histochemical demonstration of glycosidase activities is under investigation.

EXPERIMENTAL

Solvents were evaporated at reduced pressure.

1-Acetyl-3-(2′-acetamido-3′:4′:6′-tri-O-acetyl-2′-deoxy-β-D-glucosidoxy)-5-bromoindole (IV)

Acetochloroglucosamine[6] (2·7 g) and 1-acetyl-3-hydroxy-5-bromoindole[15] (1·5 g) were added to acetone (100 ml), cooled (ice-bath), and the suspension gassed for 30 min with a stream of nitrogen. N sodium hydroxide (7·4 ml) was added, and the cold mixture gassed for 1 hr. before the flask was stoppered and left to stand at 5° for 16 hr. Evaporation at room temperature yielded a greenish-brown residue which, after extensive washing with water followed by recrystallization and decolourization from ethanol, gave 1·0 g (29%) of 1-acetyl-3-(2′ acetamido-3′:4′:6′-tri-O-acetyl-2′-deoxy-β-D-glucosidoxy)-5-bromoindole, m.p. 245–246°, $[\alpha]_D^{25}$ −35·5° (*c*, 0·5 in acetone) (Found: C, 49·4; H, 4·7; N, 4·7; $C_{24}H_{27}O_{10}N_2Br$ requires: C, 49·7; H, 4·6; N, 4·8%).

[7] G. N. Bollenback, J. W. Long, D. G. Benjamin and J. A. Lindquist, *J. Amer. Chem. Soc.* **77**, 3310 (1955).
[8] F. B. Anderson and D. H. Leaback, *Chem. & Ind.* 967 (1960).
[9] G. A. Levvy, personal communication.
[10] M. S. Burstone, *J. Nat. Cancer. Inst.* **20**, 601 (1958).
[11] M. S. Burstone, *J. Nat. Cancer Inst.* **21**, 523 (1958).
[12] D. Pugh and P. G. Walker, In press.
[13] D. H. Leaback, *J. Chem. Soc.* 3166 (1960).
[14] H. H. Wotiz, E. Smakula, N. N. Lichtin and J. H. Leftin, *J. Amer. Chem. Soc.* **81**, 1704 (1959).
[15] S. J. Holt, A. E. Kellie, D. G. O'Sullivan and P. W. Sadler, *J. Chem. Soc.* 1217 (1958).

3-(2′-Acetamido-2′-deoxy-β-D-glucosidoxy)-5-bromoindole (V)

The penta-acetate (IV) (1·0 g) was suspended in dry methanol (50 ml) and N sodium methoxide (1·0 ml) added with shaking; the solid went rapidly into solution, but after a few minutes the de-acetylated compound started crystallizing. The mixture was left at 5° for 16 hr, and the solid filtered and recrystallized (harvesting the crystals as soon as possible to avoid contamination with small amounts of the indigo formed) from hot water to give 0·5 g (70%) of 3-(2′-acetamido-2′-deoxy-β-D-glucosidoxy)-5-bromoindole, m.p. 246–247°, $[\alpha]_D^{19}$ −42·0° (*c*, 0·2 in methanol) (Found: C, 46·6; H, 4·6; N, 6·8; $C_{16}H_{19}O_6N_2Br$ requires: C, 46·3; H, 4·6; N, 6·8%).

3-β-D-galactosidoxy-5-bromoindole

Acetobromogalactose was condensed as for (IV) with the indoxyl compound (II) to give a 40% yield of 1-acetyl-3-(2′:3′:4′:6′-tetra-O-acetyl-β-D-galactosidoxy)-5-bromoindole, m.p. 175–176°, $[\alpha]_D^{19}$ −26·0° (*c*, 1·0 in chloroform). This compound was deacetylated as above; the product did not crystallize from the reaction mixture, but, on evaporation and recrystallization from ethanol/chloroform, yielded 70% of 3-β-D-galactosidoxy-5-bromoindole, m.p. 195°, $[\alpha]_D^{19}$ −70·0° (*c*, 0·4 in ethanol) (Found: C, 44·9; H, 4·5; N, 3·7; $C_{14}H_{16}O_6NBr$ requires: C, 45·0; H, 4·3; N, 3·7%).

3-β-D-glucosidoxy-5-bromoindole

Acetobromoglucose was condensed as for (IV) with the indoxyl compound (II) to give a 15% yield of 1-acetyl-3-(2′:3′:4′:6′-tetra-O-acetyl-β-D-glucosidoxy)-5-bromoindole, m.p. 157–158°, $[\alpha]_D^{20}$ −47·0° (*c*, 1·0 in chloroform) which was de-acetylated as for (V) to give an 80% yield of 3-β-D-glucosidoxy-5-bromoindole, m.p. 259–260°, $[\alpha]_D^{20}$ −77·0° (*c*, 0·25 in methanol) (Found: C, 45·0; H, 4·3; N, 3·5; $C_{14}H_{16}O_6NBr$ requires: C, 45·0; H, 4·3; N, 3·7%).

Naphthalene-2-(2′-acetamido-3′:4′:6′-tri-O-acetyl-2′-deoxy-β-D-glucosidoxy)-3-carboxy-(2″:5″-dimethoxy-4″-chloro-anilide) (VI)

The naphthol derivative (III) was recrystallized from ethanol/chloroform and condensed (4·0 g) with acetochloroglucosamine[6] (4·0 g) in acetone (70 ml) in the presence of N NaOH (13 ml). After solution was complete, the mixture was allowed to stand at room temperature (16 hr) before the acetone was evaporated to leave a yellow residue, which was dissolved in chloroform (200 ml), extracted ten times with 100 ml portions of 5% NaOH and twice with water. The chloroform layer was dried and evaporated to a syrup which crystallized on the addition of ether, and which on recrystallization from ethanol gave 2·4 g (31%) of naphthalene-2-(2′-acetamido-3′:4′:6′-tri-O-acetyl-2′-deoxy-β-D-glucosidoxy)-3-carboxy-(2″:5″-dimethoxy-4″-chloro-anilide), m.p. 192° (softening 182°), $[\alpha]_D^{24}$ −51° (*c*, 1·0 in chloroform) (Found: C, 57·1; H, 5·1; N, 4·0; $C_{33}H_{39}O_{12}N_2Cl$ requires: C, 57·5; H, 5·1; N, 4·1%).

Naphthalene-2-(2′-acetamido-2′-deoxy-β-D-glucosidoxy-3-carboxy-(2″:5″-dimethoxy-4″-chloro-anilide)

The tetra-acetate (VI) (0·8 g) was suspended in dry methanol (6 ml) and N sodium methoxide (0·3 ml) added with shaking. After 16 hr at 5°, the solid was filtered off and recrystallized from 50% ethanol to give 0·5 g (76%) of naphthalene-2-(2′-acetamido-2′-deoxy-β-D-glucosidoxy)-3-carboxy-(2″:5″-dimethoxy-4″-chloro-anilide), m.p. 207°, $[\alpha]_D^{21}$ −76·8° (*c*, 0·5 in 30% dimethylformamide) (Found: C, 57·8; H, 5·2; N, 5·0; $C_{27}H_{29}O_9N_2Cl$ requires: C, 57·8; H, 5·2; N, 5·0%).

Naphthalene-2-β-D-galactosidoxy-3-carboxy-(2″:5″-dimethoxy-4″-chloro-anilide)

Acetobromogalactose was condensed as for (VI) with the naphthol derivative (III) to give a 70% yield of naphthalene-2-(2′:3′:4′:6′-tetra-O-acetyl-β-D-galactosidoxy)-3-carboxy-(2″:5″-dimethoxy-4″-chloro-anilide), m.p. 125°, $[\alpha]_D^{20}$ −75·0° (*c*, 1·0 in chloroform) which was de-acetylated as above and recrystallized from methanol to give a 65% yield of naphthalene-2-β-D-galactosidoxy-3-carboxy-(2″:5″-dimethoxy-4″-chloro-anilide), m.p. 206–207° $[\alpha]_D^{20}$ −87·0° (*c*, 0·25 in ethanol) (Found: C, 56·3; H, 5·4; N, 2·5; $C_{33}H_{39}O_9NCl.\ CH_3OH$ requires: C, 56·5; H, 5·4; N, 2·5%).

Naphthalene 2-β-D-glucuronidoxy-3-carboxy-(2″:5″-dimethoxy-4″-chloro-anilide)

Acetobromo-methyl-glucuronate was condensed as for (VI) with the napthol derivative (III) (but using two equivalents of NaOH) to give a 15% yield of naphthalene-2-(2′:3′:4′-tri-O-acetyl-β-D-glucuronidoxy methyl ester)-3-carboxy-(2″:5″-dimethoxy-4″-chloro-anilide), m.p. 154–155°, $[\alpha]_D^{20}$ −82·0° (*c*, 1·0 in chloroform) which was deacetylated and de-esterfied using barium hydroxide[14] to give a 50% yield of naphthalene-2-β-D-glucuronidoxy-(2″:5″-dimethoxy-4″-chloro-anilide), m.p. 212°, $[\alpha]_D^{20}$ −83·0° (*c*, 0·3 in ethanol) (Found: C, 56·6; H, 4·5; N, 2·7; $C_{25}H_{24}O_{10}NCl$ requires: C, 56·2; H, 4·5; N, 2·6%).

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THE STEREOCHEMISTRY OF LYCORANE—II[1]

(−)β-LYCORANE

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Abstract—Hydrogenation of diacetyllycorine (Ib) was found to be the most effective route for conversion of lycorine (Ia) into β-dihydrocaranine (II). The Hauptmann reduction of 1-deoxy-β-dihydrolycorin-2-one (XII) or the Clemmensen reduction of 1-0-acetyl-β-dihydrolycorinone (XI) followed by hydrogenation afforded (−)β-lycorane (X), which, in view of the sequence of reactions used in these transformations, is considered to have the same configurational structure as the skeleton of β-dihydrocaranine. This lycorane was also obtained by the Hauptmann reduction of β-dihydrocaranone (VIII). A procedure for preparing (−)α-lycorane (V) from 1-0-acetyllycorin-2-one (XIV) was also worked up.

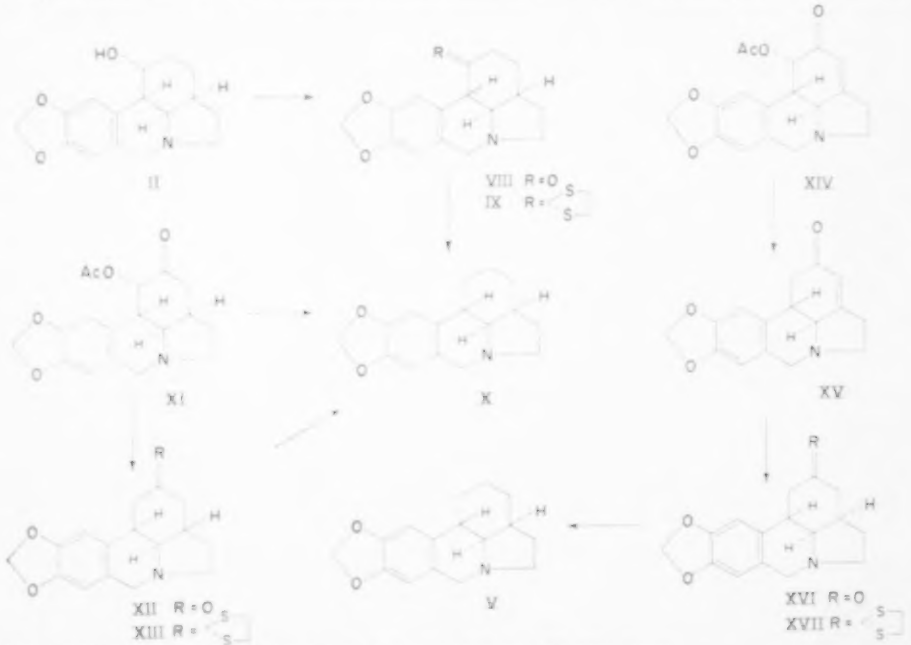
IN a preceding paper[1], we reported the preparation of (−)α-lycorane (V), which has the same configurational structure as the ring system of dihydrolycorine (VII) or α-dihydrocaranine (III).[2,3]

The author next turned to the synthesis of the lycoranes having a β-configuration at C_{3a} hydrogen.

As the starting material for this purpose, β-dihydrocaranine (II), another hydrogenation product of caranine (IV), was first considered the most suitable.

[1] Part I: K. Takeda, K. Kotera, S. Mizukami and M. Kobayashi, *Chem. Pharm. Bull.* **8**, 483 (1960).
[2] E. W. Warnhoff and W. C. Wildman, *J. Amer. Chem. Soc.* **79**, 2192 (1957); *Chem. & Ind.* 348 (1956).
[3] K. Takeda and K. Kotera, *Pharm. Bull.* **5**, 234 (1957); *Chem. & Ind.* 347 (1956).

Since, however, caranine has not yet been isolated from the bulbs of *Lycoris Radiata Herb.*, our sole natural source for obtaining the Amaryllidaceae alkaloids, it appeared at first very tedious to secure an amount of β-dihydrocaranine sufficient for the present work through the conversion of lycorine (Ia) into caranine and subsequent hydrogenation by the method reported earlier.[4] The author has, however, found a convenient procedure for the preparation of β-dihydrocaranine as follows. Hydrogenation of diacetyllycorine (Ib) with palladium–carbon in ethanol in the presence of a small amount of aqueous ammonia, followed by alkaline hydrolysis and chromatography, yielded β-dihydrocaranine in about 10 per cent yield along with small amounts of α-dihydrocaranine, caranine and (−)α-lycorane. Although the mechanism of this reduction may be complicated, it would be certain that caranine was a main intermediate formed by hydrogenolysis of the acetoxyl group allylic to the double bond in diacetyllycorine. Supporting this view, we have isolated, in a series of hydrogenation experiments carried out under a variety of conditions, caranine invariably as a by-product and in general its yields were inversely proportional to those of β-dihydrocaranine. Although convincing evidence for the formation of (−)α-lycorane as a by-product could not be obtained so far, it is possible to consider that some portion of diacetyllycorine used was converted by hydrogenolysis and simultaneous migration of the double bond[5] into acetyl isocaranine (VI) which immediately suffered further elimination of the second acetyl group attached to C_1 followed by saturation of the double bond to give (−)α-lycorane. It was shown previously that isocaranine gave on hydrogenation α-dihydrocaranine, indicating that the hydrogen atom attached to C_{3a} in isocaranine is α, like that in (−)α-lycorane.[4] It may be mentioned that in contrast to the result obtained above, catalytic reduction of



[4] K. Takeda, K. Kotera and S. Mizukami, *J. Amer. Chem. Soc.* **80**, 2562 (1958).
[5] cf. W. G. Dauben and P. D. Hence, *J. Amer. Chem. Soc.* **77**, 2451 (1955).

diacetyllycorine with Adams catalyst in acetic acid followed by alkaline hydrolysis afforded predominantly dihydrolycorine (VII), though (−)α-lycorane and α-dihydrocaranine but no β-dihydrocaranine were obtained in an extremely low yield.

An approach to the lycorane derivative of the C_{3a} β-series from β-dihydrocaranine was considered to be the oxidation of the hydroxyl group to a ketone and subsequent reduction of the carbonyl to a methylene group. Modified Oppenauer oxidation of β-dihydrocaranine using potassium t-butoxide and benzophenone furnished β-dihydrocaranone (VIII).

Although this ketone had a sharp melting point at 159–161° and the crystals apparently were homogeneous, two spots were present in the paper chromatogram using butanol–acetic acid–water (10 : 1 : 5) as a solvent system. Furthermore, catalytic reduction of the ketone in acetic acid with Adams catalyst gave three isomeric products, compounds A, B, and C which had m.p. 164–165°, 225–228° (decomp) and 217–218° (decomp), respectively, analysed for $C_{16}H_{19}O_3N$ and characterized as the respective acetates, $C_{18}H_{21}O_4N$, m.p. 196–197°, 156–156·5° and 153–154°. In this case, the ratio of the amount of compounds A, B and C isolated was 1:1:3.

One or two of the above three products were also obtained by other methods. Treatment of the ketone with lithium aluminium hydride or catalytic reduction with Adams catalyst in dry ethanol in the presence of sodium ethoxide gave compounds A and B, the isolated amount being in the ratio of 1·4 : 1 in the former case and 13:1 in the later case. However, treatment with sodium and ethanol gave only compound B. Of the three products, compound A was identical with β-dihydrocaranine, while compounds B and C were neither identical with this nor with α-dihydrocaranine.

Although attempted replacement of the hydroxyl group in these two compounds with hydrogen by treatment with thionyl chloride followed by lithium aluminium hydride or catalytic hydrogenation according to the procedure employed by Uyeo *et al.*[6] was not successful, there is no doubt that compounds B and C are stereoisomeric to β-dihydrocaranine with respect to either C_1 or C_{11b}, or to both asymmetric centres. Since the author has isolated three compounds among the four theoretically possible isomers, at least either compound B or compound C must be epimeric to β-dihydrocaranine in respect to the asymmetric centre C_{11b}. Based on these discussions together with the chromatographic finding it is obvious that β-dihydrocaranone in solutions consisted of an equilibrium mixture of epimers, formed by keto-enol tautomerism.

Conversion of the ketone into the thioketal[7] (IX) and subsequent desulphurization gave in a 28 per cent over-all yield, a new lycorane, $C_{16}H_{19}O_2N$, m.p. 72–73°, $[\alpha]_D$ −143·3° which was also characterized as its hydrochloride, m.p. 273–274° (decomp), $[\alpha]_D$ −95·9°. The base and its hydrochloride were in all respects distinctly different from (−)α-lycorane and its hydrochloride, respectively. As it is probable that this lycorane has the same configurations at all asymmetric centres as β-dihydrocaranine from the above mentioned experimental results, it was highly desirable to make clear the ambiguity as to its stereochemistry by making an approach to the same lycorane by another route which does not affect any symmetric centres in the molecule.

First, an attempt to replace the hydroxyl group in β-dihydrocaranine by a chlorine atom using thionyl chloride was not successful, since the only isolatable product was

[6] S. Uyeo, W. C. Wildman, R. J. Highet and H. M. Fales, *J. Amer. Chem. Soc.* **80**, 2590 (1958).

[7] The paper chromatography of this thioketal in the same manner as that used in β-dihydrocaranone showed only one spot, differing from that of the parent ketone and indicated the thioketal probably to be homogeneous.

an oil which contained no chlorine atom and could not be induced to crystallize. The ultra-violet spectrum indicated that it contained β-anhydrodihydrocaranine.

In contrast, 1-0-acetyl-β-dihydrolycorinone (XI) which was obtained from diacetyllycorine in three steps and established to have the same configurations as β-dihydrocaranine at C_{11b}, C_{11c} and C_{3a} by Nakagawa and Uyeo[8], was found to be useful for the synthesis of β-lycorane, having the same configurations at C_{3a}, C_{11b} and C_{11c} as β-dihydrocaranine. Treatment of this with zinc dust in acetic anhydride according to the procedure used by Woodward[9] yielded 1-deoxy-β-dihydrolycorin-2-one (XII), m.p. 165–166°. This was first converted into its thioketal (XIII) by treatment with ethanedithiol and boron fluoride–etherate and then subjected to desulphurization by refluxing with Raney nickel in methanol. The product thus obtained, (−)β-lycorane, was in every respect identical with the above-mentioned lycorane.

With the preparation of (−)β-lycorane by a sequence of reactions in which there was less chance for involvement of asymmetric centres accomplished, it is now clear that (−)β-lycorane possesses the same configurations as β-dihydrocaranine so far as the ring system is concerned.

(−)β-Lycorane was also obtained by the Clemmensen reduction of 1-0-acetyl-β-dihydrolycorinone. Since, however, a small amount of an unsaturated compound seemed to be contaminated in the product, as in the case of 6-hydroxy-7-keto-1,12-p-phenylenedodecane,[10] the crude product was hydrogenated to give pure (−)β-lycorane.

It may be added here that when 1-0-acetyllycorin-2-one (XIV)[8] was reduced with zinc dust in acetic anhydride and *o*-xylene, 1-deoxylycorin-2-one (XV) was obtained as expected. Hydrogenation of this with palladium–carbon in ethanol gave 1-deoxy-α-dihydrolycorin-2-one (XVI) which was convertible into (−)α-lycorane by reduction of its thioketal (XVII) with Raney nickel.

EXPERIMENTAL[11]

Hydrogenation of diacetyllycorine (Ib)

(a) *With Adams catalyst in acetic acid.* Diacetyllycorine (1 g) in acetic acid (55 ml) was shaken in hydrogen with Adams catalyst (150 mg) for 4 hr (hydrogen uptake: 79 ml, calc. for 1 H_2: 66 ml). After removal of the catalyst, the mixture was evaporated to dryness *in vacuo* and the residue in ethanol (100 ml) and KOH (5 g) was refluxed for 2 hr. The reaction mixture was evaporated under reduced press, dissolved in dil HCl, filtered, basified with 10% Na_2CO_3 and extracted with benzene. The solid which remained undissolved in benzene gave dihydrolycorine (VII) (305 mg), needles (from methanol), m.p. and mixed m.p. 239–240°. The infra-red spectrum was also identical with that of an authentic specimen. The dried benzene solution was evaporated to dryness under reduced press, the residue (140 mg) dissolved in benzene and chromatographed over alumina (5 g). Elution with benzene furnished on recrystallization with pet ether (−)α-lycorane (V, 22 mg), m.p. and mixed m.p. 82–83°. The infra-red spectrum in carbon disulphide solution was identical with that of an authentic specimen. Elution with 10:1 benzene–methanol gave α-dihydrocaranine (III, 25 mg), prisms (from acetone), identical with an authentic specimen in m.p., mixed m.p. (168–169°) and infra-red spectrum.

(b) *With palladium–carbon in* 95% *ethanol and ammonia.* Diacetyllycorine (2 g) in 95% ethanol (200 ml) and 28% ammomia (1 ml) was shaken in hydrogen in the presence of 10% palladium–carbon

[8] Y. Nakagawa and S. Uyeo, *J. Chem. Soc.* 3736 (1959).
[9] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. Maclamore, *J. Amer. Chem. Soc.* **74**, 4223 (1952).
[10] D. J. Cram, N. L. Allinger and H. Steinberg, *J. Amer. Chem. Soc.* **76**, 6132 (1954).
[11] All melting points are uncorrected. Unless otherwise stated, the ultra-violet spectra were taken in 95% ethanol using a Beckman Model DU spectrophotometer. Alumina used for chromatography in this experiment was Merck's Reagent Grade standardized according to the method of Brockmann. The infra-red spectra were determined with a Perkin–Elmer single-beam infra-red spectrophotometer, Model 12C, or a Koken infra-red spectrophotometer, Model, DS 301.

(3 g) for 4 hr. Hydrogen uptake was 288 ml (calc. for $2H_2$: 267 ml). After removal of the catalyst, water (30 ml) and KOH (3 g) were added and the mixture was refluxed on a water-bath for 1 hr, evaporated to dryness *in vacuo*, acidified with dil acetic acid, filtered, basified with Na_2CO_3 and extracted with benzene. The dried benzene layer was evaporated to dryness under reduced press and the residue (812 mg) in benzene–petroleum ether (1:1) was chromatographed over alumina (30 g). Elution with benzene–pet ether (1:1) and benzene gave (−)α-lycorane (V, 170 mg), prisms (from pet ether), identical with an authentic specimen in m.p., mixed m.p. and infra-red spectrum. The second benzene eluate gave β-dihydrocaranine (II, 190 mg), prisms (from ethyl acetate), identical in m.p., mixed m.p. (164–166°) and infra-red spectrum with an authentic specimen. Elution with benzene–ether (20:1, 10:1, 1:1) and ether afforded caranine (IV, 70 mg), prisms (from ethyl acetate), m.p. and mixed m.p. (177–178°). The infra-red spectrum was perfectly superimposable upon that of an authentic sample. A fraction eluted with benzene–methanol (20:1) gave on recrystallization from acetone α-dihydrocaranine (III, 25 mg) as prisms, m.p. 168–169°, identical in mixed m.p. and infra-red spectrum with an authentic specimen.

Modified Oppenauer oxidation of β-dihydrocaranine (II)

Potassium metal (100 mg) was dissolved under nitrogen in t-butanol (10 ml) which was freshly distilled over sodium metal. To the solution was added under stirring benzophenone (600 mg) and β-dihydrocaranine (200 mg), and the mixture was refluxed under nitrogen at 105–110° in an oil-bath for 2·5 hr. The excess of t-butanol was evaporated *in vacuo* over a period of 5–10 min, the residue was taken up in benzene (20 ml) and extracted repeatedly with dil HCl. The combined extracts were filtered, basified with 10% Na_2CO_3 and extracted with benzene (30 ml). The dried benzene was concentrated to 15 ml under reduced press and chromatographed over less active alumina (5 g).[13] Elution with benzene–ether (50:1) gave *β-dihydrocaranone* (VIII, 70 mg), prisms (from a small amount of benzene), m.p. 159–161°, $[\alpha]_D^{21°}$ −268·9° (*c* 0·876, chloroform), λ_{max} 290 mμ, log ε 3·66; ν_{max}^{Nujol} 1712 cm^{-1} (>C=O). (Found: C, 71·08; H, 6·54; N, 5·16. $C_{16}H_{17}O_2N$ requires: C, 70·83; H, 6·32; N, 5·16%).

From fractions eluted with benzene–ether (10:1) the starting material (20 mg) was recovered unchanged. The paper chromatography of β-dihydrocaranone by an ascending method using butanol–acetic acid–water (10:1:5) gave two spots (R_f 0·55 and 0·66) by Dragendorff's reagent.

Reduction of β-dihydrocaranone (VIII)

(a) *With lithium aluminium hydride*. β-Dihydrocaranone (65 mg) in dry ether (20 ml) was added under stirring to a suspension of lithium aluminium hydride (40 mg) in dry ether (10 ml) and the whole refluxed on 3 hr. The excess of lithium aluminium hydride was destroyed by dropwise addition of water (10 ml), the ethereal layer separated, and the aqueous layer extracted with benzene (20 ml × 2).

The combined organic layers were dried over sodium sulphate and evaporated to dryness, and the residue (67 mg) was dissolved in benzene (6 ml) and passed through a column of alumina (2 g). Elution with benzene and benzene–ether (50:1, 30:1, 10:1, 5:1) gave crude compound A (35 mg) which was recrystallized from ethyl acetate to give pure β-dihydrocaranine (II, 20 mg), m.p. 162–164°, identical in mixed m.p. and infra-red spectrum with an authentic specimen. The eluate with benzene–ether (1:1) and ether gave crude *compound* B (30 mg) which was purified by recrystallization from acetone to give scales (14 mg), m.p. 225–227° (decomp), $[\alpha]_D^{28°}$ −62·4° (*c* 0·596, ethanol), λ_{max} 237, 291 mμ, log ε 3·62, 3·68; ν_{max}^{Nujol} 3165 cm^{-1}, $\nu_{max}^{CHCl_3}$ 3600 cm^{-1} (−OH). (Found: C, 70·37; H, 7·21; N, 5·27. $C_{16}H_{25}O_3N$ requires: C, 70·31; H, 7·01; N, 5·13%).

The acetate of compound B was prepared with acetic anhydride and pyridine, m.p. 156–156·5°, needles (from ethanol), $[\alpha]_D^{21°}$ −55·8° (*c* 0·500, ethanol), λ_{max} 237, 292 mμ, log ε 3·59, 3·66; ν_{max}^{Nujol} 1731 cm^{-1} (CH_3COO—). (Found: C, 68·31; H, 6·61; N, 4·34. $C_{18}H_{27}O_4N$ requires: C, 68·55; H, 6·71; N, 4·44%).

The acetate gave compound B on hydrolysis.

(b) *With sodium and ethanol*. To a solution of β-dihydrocaranone (70 mg) in dry ethanol (20 ml) was added in portions sodium metal (850 mg) in an atmosphere of nitrogen and the mixture was

[13] Alumina used in this experiment was Merck's Reagent, the activity of which was reduced by addition of 6% water.

refluxed for 3 hr. The reaction mixture was evaporated to dryness under reduced press in nitrogen, and the residue was dissolved in water (10 ml) and extracted with benzene (45 ml). Evaporation of the dried extract gave an oil (48 mg) which was dissolved in benzene and chromatographed over alumina (5 g). Elution with benzene–ether (10:1, 5:1, 3:1) gave crude compound B (23 mg) which was recrystallized from acetone to give a pure sample (12 mg), m.p. and mixed m.p. (225–227° decomp).

(c) *With Adams catalyst in ethanol and sodium ethoxide.* β-Dihydrocaranone (50 mg) in dry ethanol (8 ml) containing sodium ethoxide (22 mg) was shaken in hydrogen with Adams catalyst (25 mg) for 3·5 hr. After removal of the catalyst the ethanol was evaporated to dryness. Water (10 ml) was added and the residue extracted with benzene. The dried benzene was evaporated, the residue dissolved in benzene and chromatographed over alumina (1·5 g). Elution with benzene–ether (50:1, 30:1, 20:1, 10:1) gave β-dihydrocaranine (II, 13 mg), m.p. and mixed m.p., 164–166°. Further elution with benzene–ether (5:1, 1:1) afforded compound B (1 mg), m.p. and mixed m.p., 225–227° (decomp).

(d) *With Adams catalyst in acetic acid.* A solution of β-dihydrocaranone (100 mg) in acetic acid (7 ml) was shaken in hydrogen with Adams catalyst (40 mg) for 4 hr. Hydrogen uptake was 9·7 ml (calcd. for 1 H_2: 8·77 ml). After removal of the catalyst, the acetic acid was evaporated to dryness and the residue was dissolved in water (5 ml), filtered, basified with Na_2CO_3 and extracted with benzene (40 ml). The dried extract was evaporated and the residue (69 mg) was chromatographed in benzene over alumina (2 g). Elution with benzene–ether (50:1, 30:1, 10:1) gave crude β-dihydrocaranine (II, 15 mg) which was recrystallized from ethyl acetate to give a pure sample (3 mg), m.p. and mixed m.p. 164–166°. The eluate with benzene–ether (5:1, 1:1) furnished crude compound B (8 mg) which on recrystallization from acetone gave a pure sample (4 mg), m.p. and mixed m.p. 225–226° (decomp). Elution with benzene–ethyl acetate (1:1) and ethyl acetate gave crude *compound* C (45 mg) which was recrystallized from ethyl acetate to give a pure sample (15 mg), m.p. 217–218°, $[\alpha]_D^{29°}$ −22·0° (*c* 0·509 ethanol), λ_{max} 238, 291 mμ, log ε 3·58, 3·66; ν_{Max}^{Nujol} 3164, 3104 cm^{-1}, $\nu_{Max}^{CHCl_3}$ 3600 cm^{-1} (−OH) (Found: C, 70·40; H, 7·29; N, 5·47. $C_{16}H_{19}O_3N$ requires: C, 70·31; H, 7·01; N, 5·13%).

The acetate was prepared with acetic anhydride and pyridine, plumes (from acetone), m.p. 153–154°, $[\alpha]_D^{21°}$ −103·7° (*c* 0·483, ethanol), λ_{max} 239, 292 mμ, log ε 3·59, 3·67; ν_{max}^{Nujol} 1741 cm^{-1} (CH_3-COO−). (Found: C, 68·54; H, 6·80; N, 4·05. $C_{18}H_{21}O_4N$ requires: C, 68·55; H, 6·71; N, 4·44%).

The acetate gave compound C on hydrolysis.

Thioketalization of β-dihydrocaranone (VIII)

Boron fluoride-etherate (0·3 ml) was added under cooling with ice to a mixture of β-dihydrocaranone (100 mg) in ethanedithiol (0·3 ml) and the mixture was allowed to stand at room temp for 20 hr. After addition of water (5 ml) and 10% NaOH (4 ml), the reaction mixture was extracted with a mixture of ether (50 ml) and benzene (10 ml), and the extract washed several times with 2% NaOH (12 ml) and then with water. The dried organic layer was evaporated to dryness under reduced press and the residue in benzene (20 ml) was chromatographed over alumina (10 g). Elution with benzene and benzene–ether (9:1) gave *thioketal* (IX, 70 mg), prisms (from ethanol), m.p. 144–145°, $[\alpha]_D^{21°}$ −64·5° (*c* 0·51 chloroform), λ_{max} 291 mμ, log ε 3·64. (Found: C, 62·30; H, 6·02; N, 4·21; S, 18·39. $C_{18}H_{21}O_2NS_2$ requires: C, 62·21; H, 6·09; N, 4·03; S, 18·46%).

In contrast to the result obtained in the case of β-dihydrocaranone, the paper chromatography of this thioketal by an ascending method using butanol–acetic acid–water (10:1:5) as a solvent system showed one spot (R_f 0·74) by Dragendorff's reagent.

Desulphurization of thioketal (IX)

Thioketal (53·1 mg) in methanol (6 ml) was refluxed with freshly prepared Raney nickel (600 mg). After removal of the catalyst, the filtrate was evaporated under reduced press and the residue in pet ether (10 ml) was chromatographed over alumina (3 g). Elution with pet ether–benzene (5:1, 4:1, 2:1, 1:1) furnished (−)*β-lycorane* (X, 20 mg), plates (from pet ether), m.p. 72–73°, $[\alpha]_D^{29°}$ −143·3° (*c* 1·04, ethanol), λ_{max} 291 mμ, log ε 3·67. (Found: C, 74·26; H, 7·53; N, 5·32. $C_{16}H_{19}O_2N$ requires: C, 74·68; H, 7·44; N, 5·44%).

Hydrochloride, needles from ethanol, m.p. 273–274° (decomp), $[\alpha]_D^{22°}$ −95·9° (*c* 0·366, chloroform). (Found: C, 64·31; H, 6·90; N, 4·65; Cl, 12·35. $C_{16}H_{19}O_2N \cdot HCl \cdot 1/4H_2O$ requires: C, 64·42; H, 6·93; N, 4·70; Cl, 11·89%).

Reaction of 1-0-*acetyl-β-dihydrolycorinone* (XI) *with zinc in o-xylene and acetic anhydride*

1-0-Acetyl-β-dihydrolycorinone (200 mg) and zinc dust (3 g) in acetic anhydride (3 ml) and dry *o*-xylene (5 ml) were refluxed under nitrogen for ½ hr. Zinc was removed and washed with benzene, the filtrate and washings were evaporated to dryness *in vacuo* and the residue was dissolved in dil HCl, filtered, basified with Na_2CO_3 and extracted with benzene. The dried benzene layer was evaporated under reduced press and the residue (124 mg) dissolved in benzene was chromatographed over alumina (4 g). Elution with benzene gave 1-*deoxy-β-dihydrolycorin-2-one* (XII, 55 mg), plates after repeated crystallizations from ethanol, m.p. 165–166°, $[\alpha]_D^{16°}$ −78·4° (*c* 0·589, ethanol), λ_{max} 291 mμ, log ε 3·68; ν_{Max}^{Nujol} 1711 cm^{-1} ( ). (Found: C, 70·96; H, 6·44; N, 5·27. $C_{16}H_{17}O_3N$ requires: C, 70·83; H, 6·32; N, 5·16%).

Thioketalization of 1-*deoxy-β-dihydrolycorin-2-one* (XII)

To a mixture of 1-doxy-β-dihydrolycorin-2-one (50 mg) and ethanedithiol (0·2 ml) was added boron fluoride-etherate (0·2 ml) under cooling with ice. The mixture was kept at room temp for 16 hr. Water (5 ml) and 10% NaOH (4 ml) were added and the whole was extracted with a mixture of ether (40 ml) and benzene (10 ml). The extract was washed with 10% NaOH (2 ml) and water (10 ml), dried with anhyd sodium sulphate and evaporated to dryness under reduced press. The residue (50 mg) in pet ether–benzene (3:1) was chromatographed over alumina (1·5 g). Elution with pet ether–benzene (3:1, 2:1) gave *thioketal* (XIII, 34 mg), needles (from ether), m.p. 117–118°, $[\alpha]_D^{22°}$ −94·4° (*c* 0·566, ethanol), λ_{max} 291 mμ, log ε 3·76. (Found: C, 62·61; H, 6·12; N, 3·97; S, 18·49. $C_{18}H_{21}O_2NS_2$ requires: C, 62·21; H, 6·09; N, 4·03; S, 18·45%).

Desulphurization of thioketal (XIII)

Thioketal (57 mg) in methanol (4 ml) was refluxed with freshly prepared Raney nickel (500 mg) for 4 hr. After filtration of the catalyst and concentration of the filtrate, the residue (29 mg) in pet. ether–benzene (1:1) was chromatographed over alumina (1 g). Elution with pet ether–benzene (1:1) gave (−)β-lycorane (X, 17 mg), plates (from pet ether), m.p. 72–73°, $[\alpha]_D^{16°}$ −143·0° (*c* 0·57, ethanol), λ_{max} 291 mμ, log 3·67. A mixed m.p. of this with (−)α-lycorane (V) was depressed to 53–59° and the infra-red spectrum was not identical with that of V. (Found: C, 74·50; H, 7·52; N, 5·74. Calcd. for $C_{16}H_{19}O_2N$: C, 74·68; H, 7·44; N, 5·44%).

Clemmensen reduction of 1-0-*acetyl-β-dihydrolycorinone* (XI) *and hydrogenation of the product with Adams catalyst*

1-0-Acetyl-β-dihydrolycorinone (300 mg) in conc HCl (6 ml) was added dropwise to zinc-amalgam (1·5 g) which was prepared by amalgamating zinc (1·5 g) with mercuric chloride (276 mg) in water (4·8 ml) and conc HCl (1·8 ml). The mixture was stirred at 60–70° for 3 hr. After filtration, the filtrate was made alkaline with Na_2CO_3, extracted with a mixture of benzene–ether and the dried extract evaporated to dryness under reduced press. The residue (145 mg) in ethyl acetate (4 ml) was shaken in hydrogen with Adams catalyst (40 mg) for 2 hr. After filtration of the catalyst and evaporation of the filtrate, the residue was dissolved in dil HCl, filtered, basified with Na_2CO_3 and extracted with pet ether. The dried organic layer was evaporated and the residue (61 mg) in pet ether–benzene (2:1) passed through a column of alumina (3 g). A pet ether–benzene (2:1) eluate gave (−)β-lycorane (X, 25 mg), plates (from pet ether), m.p. 72–73°, identical in m.p., mixed m.p. and infra-red spectrum with the sample mentioned above.

Reaction of 1-0-*acetyl-lycorin-2-one* (XIV) *with zinc in o-xylene and acetic anhydride*

1-0-Acetyl-lycorin-2-one (200 mg) was dissolved in dry *o*-xylene (3 ml) and acetic anhydride (2 ml) under heating at 145–150° in an oil-bath, zinc dust (2 g) was added in one portion to the solution and the mixture was refluxed under nitrogen for 8 min. After removal of zinc the filtrate and washings were evaporated to dryness *in vacuo* and the residue was dissolved in dil acetic acid, filtered, basified with Na_2CO_3 and extracted with benzene–ether (1:1). The dried extract was evaporated under reduced press and the residue (130 mg) gave, on repeated crystallizations from acetone, 1-*deoxy-lycorin-2-one* (XV, 50 mg) as colourless needles, m.p. 157–158° (decomp), $[\alpha]_D^{24°}$ −169° (*c* 0·490, dioxane), λ_{max} 231, 290 mμ, log ε 4·20, 3·70; ν_{Max}^{Nujol} 1664 cm^{-1} (α,β-unsaturated ketone). (Found: C, 71·35; H, 5·65; N, 4·99. $C_{16}H_{13}O_3N$ requires: C, 71·36; H, 5·61; N, 5·20%).

Hydrogenation of 1-*deoxy-lycorin-2-one* (XV) *with palladium–carbon in ethanol and dioxane*

1-Deoxy-lycorin-2-one (92 mg) in ethanol (3 ml) and dioxane (4 ml) was shaken in hydrogen in the presence of 15% palladium-on-carbon (200 mg) for 5 hr (hydrogen uptake: 8·7 ml, calc. for 1 H_2: 7·6 ml). After removal of the catalyst, the filtrate was evaporated, the residue dissolved in dil HCl, filtered, made alkaline with Na_2CO_3 and extracted with benzene. The dried benzene was evaporated under reduced press and the residue (42 mg) in benzene–pet ether (1:1, 5 ml) chromatographed over alumina (2 g). Elution with benzene–pet ether (7:3) gave 1-*deoxy*-α-*dihydrolycorin-2-one* (XVI, 30 mg), plates (from acetone), m.p. 147–148°, $[\alpha]_D^{21°}$ −234·4° (*c* 0·748 ethanol), λ_{max} 292 mμ, log ε 3·67; ν_{max}^{Nujol} 1711 cm^{-1} (>C=O). (Found: C, 70·82; H, 6·39; N, 5·01. $C_{16}H_{17}O_3N$ requires: C, 70·83; H, 6·32; N, 5·16%).

Thioketalization of 1-*deoxy*-α-*dihydrolycorin-2-one* (XVI)

1-Deoxy-α-dihydrolycorin-2-one (103 mg) was treated in the usual manner with ethandithiol (0·3 ml) and boron fluoride-etherate (0·3 ml) to give the *thioketal* (XVII, 80 mg). It formed needles (from ether), m.p. 107–108°, $[\alpha]_D^{26°}$ −37·5° (*c* 0·787, ethanol), λ_{max} 292 mμ, log ε 3·69. (Found: C, 62·42; H, 6·13; N, 3·89; S, 18·18. $C_{18}H_{21}O_2NS_2$: C, 62·21; H, 6·09; N, 4·03; S, 18·46%).

Desulphurization of thioketal (XVII)

Thioketal (56 mg) in methanol (5 ml) was refluxed with Raney nickel (600 mg) for 5 hr. After working up in an usual manner, the product (13 mg) was chromatographed in benzene–pet ether (1:1, 4 ml) over alumina (1 g). Elution with benzene–pet ether (1:1) gave (−)α-lycorane (V, 8 mg), m.p. 82–83°, plates (from pet ether), identical in m.p., mixed m.p. and infra-red spectrum with an authentic specimen.

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THE STEREOCHEMISTRY OF LYCORANE—III[1]

γ- AND δ-LYCORANE

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Abstract—Hydrogenation of α-anhydrodihydrocaranine (V) or anhydrocaranine (VII) with Adams catalyst in acetic acid or the Hauptmann reduction of α-dihydrocaranone (XX) yielded (−)γ-lycorane (XVII). Catalytic reduction of β-anhydrodihydrocaranine (IX) with palladium-carbon in ethanol gave (+)γ-lycorane (XVIII), while with Adams catalyst in acetic acid it afforded (+)δ-lycorane (XIX) along with (−)β-lycorane (III). Reduction of anhydrocaranine in ethanol gave (±)γ-lycorane which was also obtained by hydrogenation of anhydrolycorine (X). Based on these findings, the configurational structures of α-, β-, γ- and δ-lycorane were established and the configuration of dihydrolycorine was confirmed.

IN previous papers,[2] Takeda and Kotera have advanced the stereostructure I or its mirror image for dihydrolycorine. That the B/C ring juncture is *trans* in this compound, was based on the fact that α-dihydrocaranine (IV) readily lost a molecule of water to give α-anhydrodihydrocaranine (V) presumably due to a *trans* elimination of the hydroxyl group at C_1 and the hydrogen atom located at C_{11b}. However, there was encountered an occasion where the B/C rings might be supposed to be *cis*-fused, since

[1] Part II: K. Kotera, *Tetrahedron* **12**, 240 (1961).
[2] K. Takeda and K. Kotera, *Chem. & Ind.* 347 (1956); *Pharm. Bull.* **5**, 234 (1957).

the hydrogen atoms linked to C_{11b} and C_{11c} could be eliminated quite readily by selenium oxide.[3] In order to obtain confirmatory evidence for the configuration of the B/C ring juncture in dihydrolycorine and to establish the stereochemistry of lycoranes, which had been derived from the former or related compounds, the author has carried out a series of reactions which is the subject of the present paper.

Of the four possible stereoisomeric pairs of lycoranes, which contain three asymmetric centers, (−)α- and (−)β-lycorane were reported in the previous paper[1,4] and shown to represent the skeleton of dihydrolycorine or α-dihydrocaranine and that of β-dihydrocaranine, respectively. Isomeric lycoranes have been obtained from α-dihydrocaranine (IV) or β-dihydrocaranine (VIII) by the following procedure.

Hydrogenation of α-anhydrodihydrocaranine (V) with either Adams catalyst in acetic acid or palladium–carbon in ethanol gave a homogeneous oil which was convertible in good yield into its hydrochloride, $C_{16}H_{19}O_2N{\cdot}HCl$, m.p. 256° (decomp), $[\alpha]_D$ −15·0°. Although the melting point of this salt was very close to that of (−)α-lycorane hydrochloride, a mixed melting point and the infra-red spectra indicated clearly that they are not identical. The free base regenerated from its purified hydrochloride was not crystalline and its optical rotation $[\alpha]_D$ −17·1° and infra-red spectrum were distinctly different from those of (−)α-lycorane or (−)β-lycorane. It was certain, therefore, that with this compound the author had a new isomer of lycorane which was named (−)γ-lycorane. The same lycorane was also obtained by hydrogenation of anhydrodihydrolycorine (VI) or anhydrocaranine (VII)[5] in acetic acid over Adams catalyst.

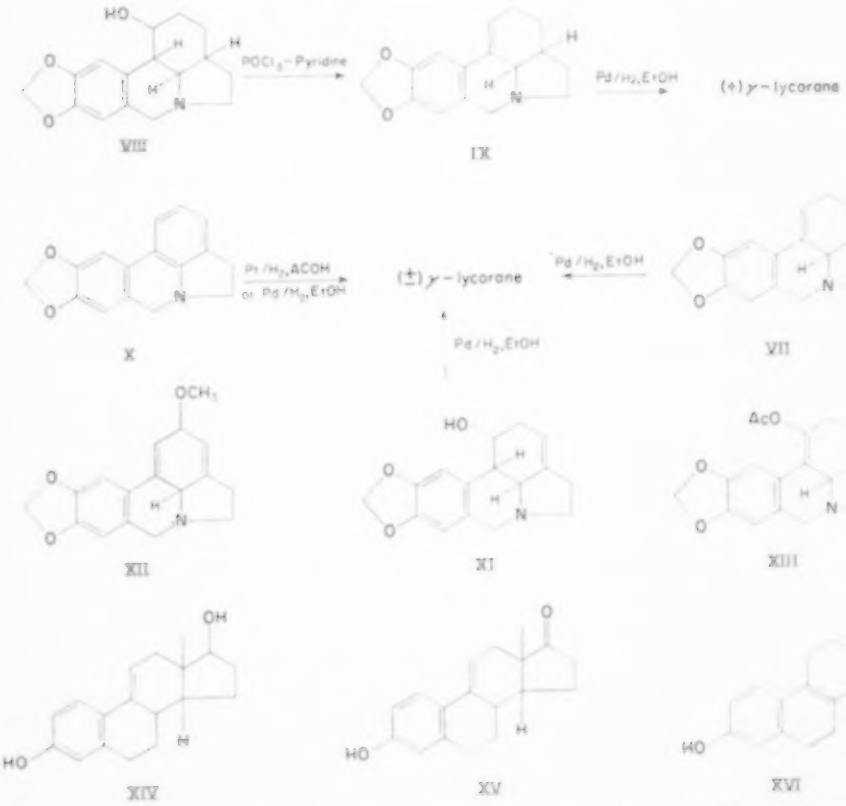
Next, the author investigated the hydrogenation of β-anhydrodihydrocaranine which was prepared from β-dihydrocaranine (VIII)[6] by the same method as used for the preparation of its α-isomer and assigned the analogous structure (IX). Treatment of β-anhydrodihydrocaranine with hydrogen and palladium–carbon in ethanol furnished an oil, $[\alpha]_D$ +16·2°, which was convertible in good yield into its hydrochloride, $C_{16}H_{19}O_2N{\cdot}HCl$, m.p. 255–256° (decomp), $[\alpha]_D$ +13·3°. The infra-red spectra of the free base as well as its hydrochloride were identical with those of (−)γ-lycorane and its hydrochloride, respectively. Since the optical rotations of the corresponding derivatives were almost the same in value but opposite in direction, it was highly probable that this hydrogenation product, (+)γ-lycorane, was an enantiomorph of (−)γ-lycorane. As expected, a mixture of equivalent weights of (−)γ-lycorane and (+)γ-lycorane yielded a racemate, (±)γ-lycorane, m.p. 101–102°, which showed no optical rotation. The same racemate was also obtained by hydrogenation of anhydrolycorine (X) in acidic or ethanol solution in the presence of Adams catalyst or palladium–carbon at a temperature not higher than 60°. Furthermore, hydrogenation of anhydrocaranine and even caranine (XI)[5,6] itself with palladium–carbon in ethanol furnished (±)γ-lycorane, albeit in a very small yield in the latter case.

Since convincing evidence has been accumulated[2,5,6] that α- and β-dihydrocaranine, IV and VIII, have the same stereostructure except for the configuration of ring C/D juncture, which is *cis* in the former and *trans* in the latter compound, and the location of the double bond in α- and β-anhydrodihydrocaranine is evidently at $C_1 - C_{11b}$ as shown in the Table 1, an essential feature of the hydrogenation of α- and

[3] H. M. Fales, L. D. Giuffrida and W. C. Wildman, *J. Amer. Chem. Soc.* **78**, 4145 (1956).
[4] K. Takeda, K. Kotera, S. Mizukami and M. Kobayashi, *Chem. Pharm. Bull.* **8**, 483 (1960).
[5] K. Takeda, K. Kotera and S. Mizukami, *J. Amer. Chem. Soc.* **80**, 2562 (1958).
[6] E. W. Warnhoff and W. C. Wildman, *Chem. & Ind.* 348 (1956); *J. Amer. Chem. Soc.* **79**, 2192 (1957).

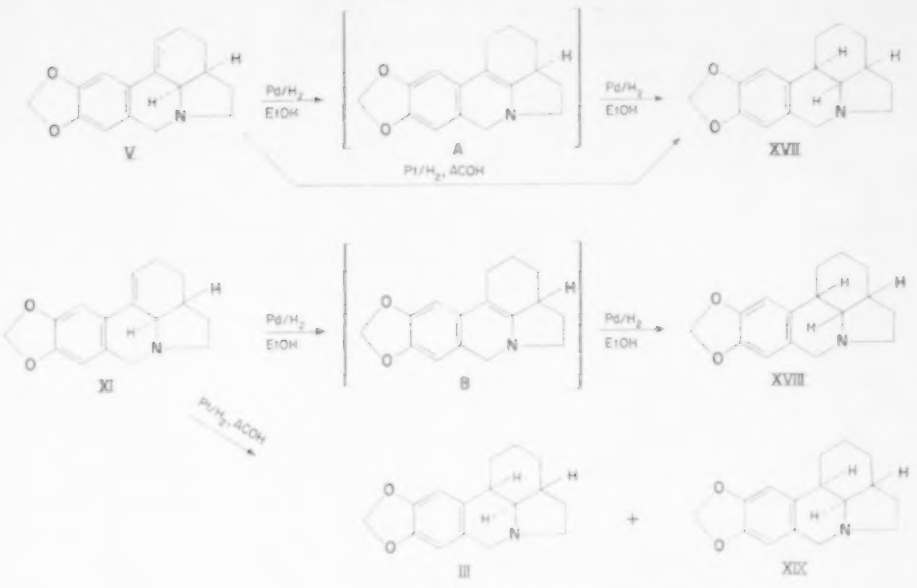
TABLE 1. DATA OF ULTRA-VIOLET SPECTRA OF ANHYDRODIHYDROCARANINES AND RELATED COMPOUNDS

Compound	log	mμ
α-Anhydrodihydrocaranine (V)[2]	4·12	263
β-Anhydrodihydrocaranine (IX)	4·17	266
Anhydrocaranine (VII)[5]	4·06	265
2-Methoxyanhydrocaranine (XII)[5]	4·08	266
α-Dihydrocaranone enolacetate (XIII)[6]	4·08	265
9-Dehydro-14-isoestradiol-17β (XIV)[7]	4·25	264
9-Dehydro-14-isoestrone (XV)[7]	4·26	264
8-Dehydro-14-isoestrone (XVI)[7]	4·32	275



β-anhydrodihydrocaranine, V and IX, is the formation of a pair of enantiomorphic compounds from diastereoisomers. In order to accommodate the experimental results as mentioned above, a migration of the double bond in one or both of the anhydrodihydrocaranines to the position between C_{11b} and C_{11c} followed by *cis*-addition of hydrogen atoms to the double bond from the back side of the ethylenic residue linked to ring C were necessary as shown in the following chart.

[7] L. F. Fieser and M. Fieser, *Steroids* p. 462. Reinhold, New York (1959).



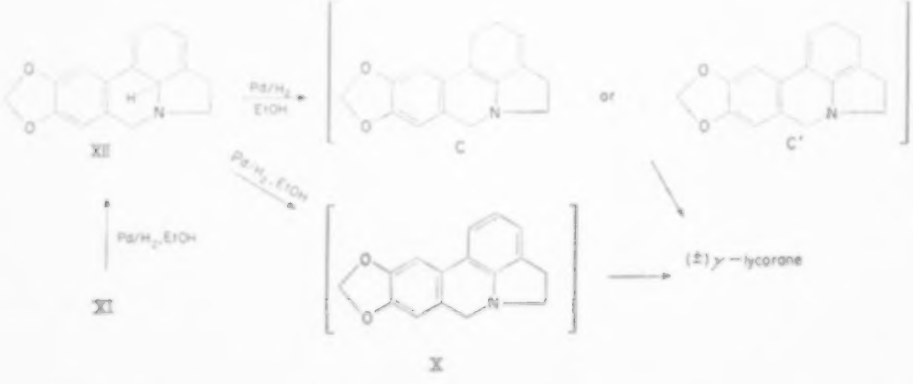
If the migration of the double bond in α- and β-anhydrodihydrocaranines to the 11b, 11c-position as in A or B did not precede the hydrogenation, the resulting lycoranes obviously are not enantiomeric, since the asymmetric centre at C_{11c} is in the same configuration while that at C_{3a} is enantiomeric in this pair of starting materials.

For the sake of convenience, the author would assume that the shift of the double bond took place in both anhydrodihydrocaranines giving enantiomeric A and B, as intermediates, then it would be readily conceivable that saturation of the respective double bonds gave rise to a pair of enantiomeric γ-lycoranes, whatever the mode of addition of hydrogen atoms may be. As to this, it has been accepted generally that *cis* addition is predominantly involved in the catalytic hydrogenation at low temperatures. Since the conditions used by the author for the preparation of these lycoranes were at room temperature or at temperatures not higher than 60°, it would be highly plausible that hydrogen added *cis* to A and B either from the back side or from the front side of the ethylenic residue linked to ring C. Of these possibilities, the front side attack of hydrogen to A and B can be ruled out experimentally based on the fact that anhydrocaranine gave optically active (−)γ-lycorane on hydrogenation in acetic acid. This reduction showed that no compound such as the product C or C′ of double bond migration or dehydrogenation product X is an intermediate and, most important, that C_{11c} in (−)γ-lycorane has the same configuration as in α- or β-dihydrocaranine or dihydrolycorine. Since hydrogenation of α-anhydrodihydrocaranine leading to the same lycorane did not affect the configuration of C_{3a} which is the same as that of α-dihydrocaranine or dihydrolycorine, even if the double bond migration took place during the reduction procedure, the hydrogen atoms at C_{3a} and C_{11c} in (−)γ-lycorane must have the same configuration as those in dihydrolycorine and are *cis* to each other. Accordingly it is clear that the hydrogen atoms is added to α-anhydrodihydrocaranine or to the intermediate A of double bond migration from the same α-side as that of the hydrogen atom attached at C_{3a} as in the case of anhydrocaranine. Since this must be

the case in the rearrangement product B of β-anhydrodihydrocaranine, the hydrogen atoms at C_{3a}, C_{11b} and C_{11c} in γ-lycoranes are most likely on the same side of ring C. Based on these discussions it was concluded that both rings B/C and C/D are very probably *cis*-fused in γ-lycoranes.

Although the shift of the double bond mentioned above is prerequisite for the conversion of β-anhydrodihydrocaranine into (+)γ-lycorane, it is not always necessary for the transformation of α-anhydrodihydrocaranine to (−)γ-lycorane, since the C/D rings are *cis*-fused in both of the latter compounds. In the latter case, an assumption that hydrogen atoms directly attacked α-anhydrodihydrocaranine from the rear side of the axial ethylenic side chain would be sufficient for explaining the path. The author considers, however, that α-anhydrodihydrocaranine was hydrogenated to give (−)γ-lycorane through the intermediate A in ethanol solution over palladium–carbon in an analogous manner as β-anhydrodihydrocaranine, while in acetic acid solution over Adams catalyst it was directly reduced like anhydrocaranine without precedence of any double bond shift. Supporting this view β-anhydrodihydrocaranine was catalytically reduced in acetic acid in the presence of Adams catalyst to give two compounds which were separated by chromatography into (−)β-lycorane and a new lycorane. (−)β-Lycorane thus obtained was characterized as its hydrochloride which was identical in all respects with an authentic sample of (−)β-lycorane hydrochloride reported in the preceding paper.[1] The other lycorane had m.p. 125–127°, $[\alpha]_D$ +48·0 and was analysed correctly for $C_{16}H_{19}O_2N$. Since this was not identical with any of the lycorane isomers so far obtained, it was designated as (+)δ-lycorane. If in this case the double bond migration took place during the hydrogenation, one of the products should be identical with (+)γ-lycorane.

The formation of (±)γ-lycorane from anhydrolycorine can be explained by assuming one-sided addition of hydrogen atoms to the aromatic ring C from either side of the ring, as considered highly probable in catalytic hydrogenation of benzenoid rings under mild conditions.[8]



Analogously the conversion of anhydrocaranine into (±)γ-lycorane by hydrogenation in a neutral medium would be explainable by assuming an intermediate C or

[8] R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine and R. R. Whetstone, *J. Amer. Chem. Soc.* **64**, 1985 (1942).

C′ or through its dehydrogenation to anhydrolycorine, all of which lack any asymmetric centre and obviously give rise to racemic γ-lycorane on one-sided addition of hydrogen atoms to the double bonds.

The formation of (±)γ-lycorane in a very low yield from caranine would be interpreted as a result of dehydration of a small portion of the base during the hydrogenation under the conditions used by the author, affording anhydrocaranine as an intermediate.

Very recently Nakagawa and Uyeo[9] have established that the absolute configuration of the hydroxyl group attached to C_2 of lycorine or dihydrolycorine is β-oriented. Since the ethylenic residue attached to ring C in dihydrolycorine is on the same side as that of this hydroxyl and its configuration was obviously retained in (−)γ-lycorane as discussed above, the absolute configuration of (−)γ- and (+)γ-lycorane would be best represented by formulations XVII and XVIII, respectively.

VOL. 12 1961

It is remarkable that (−)γ-lycorane was also derived from α-dihydrocaranine by an alternative route. α-Dihydrocaranone[6] (XX) which was obtainable from α-dihydrocaranine by the modified Oppenauer oxidation was first converted into its thioketal XXI in the usual manner and then subjected to desulphurization by heating with Raney nickel. The resulting oil was found to be identical with (−)γ-lycorane. This result would be explainable only by assuming that an epimerization had taken place completely at the hydrogen atom attached to C_{11b} during the oxidation procedure to the ketone, as a result of keto-enol tautomerism especially in an alkaline solution.

Supporting this view, α-dihydrocaranone showed only one spot (*Rf* 0·58) by paper chromatography using butanol–acetic acid–water (10:1:5) as a solvent system. Furthermore, treatment of this with lithium aluminium hydride gave two isomeric compounds D and E, $C_{16}H_{19}O_3N$, which had m.p.s. 110–111° and 150–151° respectively, and were also characterized as the respective acetates, $C_{18}H_{21}O_4N$, m.p.s 95–96° and 85–86°.

These two compounds were also obtained by catalytic reduction of α-dihydrocaranone with Adams catalyst in acetic acid. On reduction with sodium in ethanol, on the other hand, the only isolatable product was compound E. Neither compound D nor E was identical with α-dihydrocaranine which would be expected to occur in the reduction mixture, if the initial oxidation product of α-dihydrocaranine did not undergo any epimerization.

These results indicated that the ketone XX is, in contrast to β-dihydrocaranone,[1] homogeneous and not an equilibrium mixture, and the reduction products are epimers only with respect to the asymmetric centre at C_1. The mode of reduction of the ketone and the fact that compound D was more easily eluted than compound E on chromatography over alumina suggested that the configuration of the hydroxyl group in compound D is probably axial, while that in compound E equatorial. Compounds D and E were named, therefore, 1-epi-γ-dihydrocaranine and γ-dihydrocaranine and assigned configurational structures XXII and XXIII, respectively. Conversion of 1-epi-γ-dihydrocaranine into a lycorane was not successful, but the treatment of γ-dihydrocaranine with thionyl chloride gave a chloro-compound XXIV which afforded on catalytic reduction with Adams catalyst in ethanol, as expected, (−)γ-lycorane.

With the configuration of (−)γ- and (+)γ-lycorane established, the author can now deduce the stereochemistry of (−)α-, (−)β- and (+)δ-lycorane.

[9] Y. Nakagawa and S. Uyeo, *J. Chem. Soc.* 3736 (1959).

Since in the course of transformations of α-dihydrocaranine to (−)γ-lycorane by the route mentioned above, any inversion cannot be expected to take place at the asymmetric centres other than that at C_{11b} and (−)α-lycorane no doubt retains original configurations of the skeleton of α-dihydrocaranine as reported previously,[8] two lycoranes are different stereochemically only in the configuration at C_{11b}. Based on the established configuration of (−)γ-lycorane it can be concluded, therefore, that (−)α-lycorane has a *trans*-B/C and a *cis*-C/D junction, as formulated as II, and it is clear that the stereochemistry of dihydrolycorine is I, supporting the previous view.[2]

It has been shown previously that α- and β-dihydrocaranine are stereoisomers with respect to the asymmetric centre at C_{3a}. Since (−)β-lycorane is comparable in configurations to the skeleton of β-dihydrocaranine, it can only be represented by III, having a *trans*-B/C and a *trans*-C/D ring junction.

As to the stereochemistry of (+)δ-lycorane, it is obvious that it is an epimer of (−)β-lycorane with respect to the configuration at C_{11b}, as represented by the formula XIX. Thus the author has established the stereochemistry of all of the possible lycorane isomers, α-, β-, γ- and δ-lycorane.

Finally, the author would like to discuss briefly some problems which were encountered during the course of the present studies. First the fact that α-anhydrodihydrocaranine gave on hydrogenation with Adams catalyst in acetic acid solely (−)γ-lycorane, while β-anhydrodihydrocaranine furnished under the similar conditions two hydrogenation products, (−)β-lycorane and (+)δ-lycorane, may be explained by assuming that the hydrogenation occurred preferently on the α-face of the former compound due to serious shielding effect of the β-oriented axial ethylenic bond attached to ring C. In contrast to this, β-anhydrodihydrocaranine is nearly planar and neighbouring hydrogen atoms can therefore attack the double bond from both sides of the molecule, giving a pair of epimeric dihydro-compounds.

The second problem is concerned with the configurational assignment of α- and β-dihydrocaranone. As to the stability of the B/C ring juncture in such a hydrophenanthridine ring system containing an aromatic ring A, little is known so far. It has

XXV XXVI

recently been reported,[10,11] however, that compounds XXV and XXVI having B/C *cis* structures are more stable than the B/C *trans* isomers or at least of similar stability due to more serious non-bonded interactions between C_1 and C_{11} and between C_7 and C_{14} in the latter than in the former. If this is also the case in α- and β-dihydrocaranone, the non-bonded interaction may have caused an epimerization of the hydrogen atom attached to C_{11b} under the alkaline conditions of the Oppenauer method giving rise predominantly to compounds having B/C *cis* configuration, since the starting materials leading to these ketones had *trans*-fused B/C rings. Experimental results have indicated that α-dihydrocaranone has *cis*-fused B/C rings, while the β-isomer is an equilibrium mixture consisting of epimers having B/C rings in *cis* and *trans* configuration.

XXVII XXVIII

XXIX XXX

In α-dihydrocaranone, the benzene ring can take up the stable equatorial even after the epimerization at C_{11b} took place to decrease the non-bonded interaction between C_1 and C_{11}, since ring C and D are *cis*-fused and ring conversions are free. The *cis-trans* equilibrium of the B/C ring juncture is therefore greatly in favour of the *cis*-form (XXVIII) and not the *trans*-form (XXVII). On the other hand, in β-dihydrocaranone, conversion of ring C is not possible, ring C and D being *trans*-fused. If epimerization occurred in this, the benzene ring which was originally equatorial with respect to ring C will have to take up an axial position, the steric effect of which will unfavourably affect the epimerization at C_{11b}, resulting in existence of a pair of epimers, XXIX and XXX, in equilibrium in solutions.

The last problem to be discussed is the infra-red spectra of four lycoranes, isolated by the author. Recently Bohlmann[12] found that the *trans*-quinolizidine (XXXI) showed characteristic bands in the 2700–2800 cm^{-1} region which were lacking in the *cis*-quinolizidine (XXXII). This finding has been confirmed in a variety of alkaloids

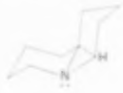
[10] W. Johnson, I. David, H. Dehm, R. Height, E. Wannhoff, W. Wood, and E. Johnes, *J. Amer. Chem. Soc.* **80**, 661 (1958).

[11] J. Elks, J. E. Oughton and L. Stephenson, *Proc. Chem. Soc.* 6 (1959).

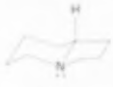
[12] F. Bohlmann, *Chem. Ber.* **91**, 2157 (1958); F. Bohlmann and C. Arndt, *Ibid.* **91**, 2167 (1958); F. Bohlmann, W. Weise, D. Rahtz and C. Arndt, *Ibid.* **91**, 2176 (1958); F. Bohlmann, E. Winterfeldt and H. Brackel, *Ibid.* **91**, 2194 (1958).

and also applied to the other alkaloids for establishment of their stereochemistry. Since lycoranes have a pyrrocolidine ring system in the molecule in place of a quinolizidine, it seemed to be interesting to examine whether Bohlmann's rule is applicable to the steric structures of lycoranes proposed by the author, infra-red spectra of four

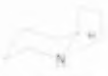
XXXI



XXXII

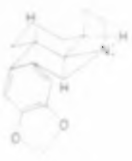


XXXIII



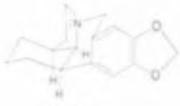
XXXIVa

XXXIVb



XXXV

XXXVI



XXXVII

XXXVIII

lycoranes in carbon disulphide were compared with one another especially in the 2700–2800 cm^{-1} region. As shown in Fig. 1, it was found that both (−)β-lycorane (XXXVI) and (−)γ-lycorane (XXXVII), having a *trans*-pyrrocolidine ring XXXIII, exhibited characteristic bands in the 2700–2800 cm^{-1} region, but (+)δ-lycorane (XXXVIII), having *cis*-pyrrocolidine XXXIVa or XXXIVb, did not show bands in the corresponding region. It appeared abnormal that (−)α-lycorane (XXXV) showed a band at 2783 cm^{-1}, since this should have a *cis*-pyrrocolidine ring in the molecule.

EXPERIMENTAL[13]

(−)γ-*Lycorane* (XVII)

(a) *From* α-*anhydrodihydrocaranine* (V). Hydrogenation of α-anhydrodihydrocaranine (100 mg) over Adams catalyst (20 mg) in acetic acid (7 ml) was complete in 2 hr after 0·9 equivalent of hydrogen had been taken up. The hydrogenation product was chromatographed on alumina (5 g), and pet ether eluate gave (−)γ-*lycorane* (XVII, 65 mg) as an oil which was dried in a vacuum to a constant weight. $[\alpha]_D^{20°}$ −17·1° (*c* 0·25, ethanol). (Found: C, 74·90; H, 7·44; N, 5·20. $C_{16}H_{19}O_2N$ requires: C, 74·68, H, 7·44; N, 5·44%).

[13] All m.p.s are uncorrected. Unless otherwise stated, the ultra-violet spectra were taken in 95% ethanol using a Beckman Model DU spectrophotometer. Alumina used for chromatography in this experiment was Merck's Reagent Grade standardized according to the method of Brockmann. The infra-red absorption spectra were determined with a Perkin–Elmer Model 12C Single-beam Infra-red Spectrophotometer.

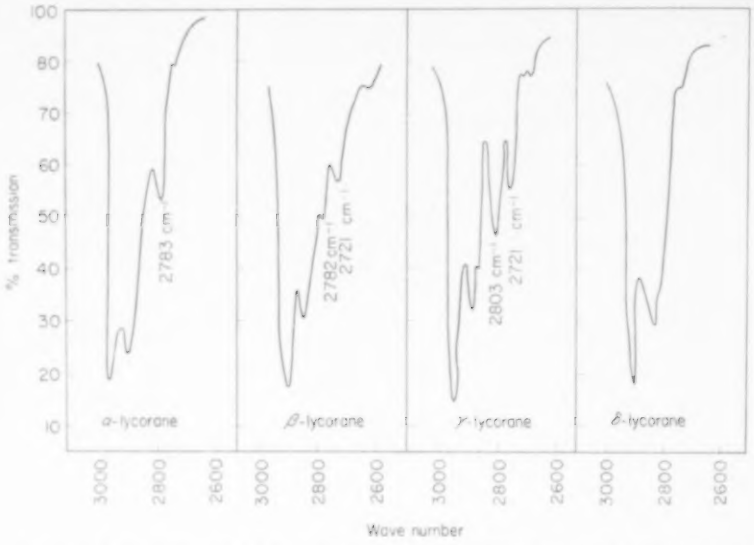


FIG. 1. Infra-red spectra of four isomeric lycoranes at 3000–2600 cm^{-1} in carbon disulphide solution.

The hydrochloride formed needles from water, m.p. 255–256° (decomp), $[\alpha]_D^{20°}$ −15·0° (*c* 1·00, ethanol), λ_{max} 290 mμ (log ε 3·70). (Found: C, 65·56; H, 6·89; N, 4·89. $C_{16}H_{19}O_2N$·HCl requires: C, 65·39; H, 6·86; N, 4·77%).

The infra-red spectra of (−)γ-lycorane (XVII) and (−)α-lycorane in carbon disulphide solution were not identical. The mixed m.p. of the hydrochlorides of (−)γ-lycorane and (−)α-lycorane was depressed to 237–247° (decomp).

Hydrogenation of α-anhydrodihydrocaranine (100 mg) in ethanol (100 ml) with 10% palladium–charcoal (150 mg) was complete in 7 hr when 1·2 equivalent of hydrogen had been taken up. The catalyst was removed by filtration and most of the solvent was evaporated. The residue was dissolved in dil HCl, filtered, made alkaline with Na_2CO_3 and extracted with pet ether. Concentration of the dried extract gave an oil (71 mg), identical with (−)γ-lycorane (XVII) by comparison of the infra-red spectra in carbon disulphide solution. Furthermore, the hydrochloride, m.p. 255–256° (decomp), was also identical with that of (−)γ-lycorane in m.p., mixed m.p. and infra-red spectrum.

(b) *From anhydrocaranine* (VII). A solution of anhydrocaranine (300 mg) in acetic acid (30 ml) was shaken in hydrogen in the presence of Adams catalyst (180 mg) at 50–60°. Theoretical amounts of hydrogen were absorbed in 11 hr. After evaporation of acetic acid under reduced press, the residue was dissolved in water, filtered, basified with 10% Na_2CO_3 and extracted with benzene. The benzene extract was shaken with 5% HCl and the aqueous acidic layer made alkaline with 10% Na_2CO_3 and extracted again with benzene. Concentration of the dried extract gave an oil (240 mg) which was chromatographed over alumina (20 g). Pet ether eluate gave an oil (150 mg) which was identical in infra-red spectrum in carbon disulphide solution with (−)γ-lycorane (XVII) obtained above. The hydrochloride, m.p. 255–256° (decomp), was also identical in m.p., mixed m.p. and infra-red spectrum with that of XVII.

(c) *From anhydrodihydrolycorine* (VI). A solution of anhydrodihydrolycorine (20 mg) in acetic acid (1 ml) was shaken in hydrogen in the presence of Adams catalyst (2 mg). Hydrogenation was complete in 5 hr after 1 mole of hydrogen was absorbed. The hydrogenation product was worked up in the usual manner and an oil (14 mg) was obtained, whose infra-red spectrum was identical with that of (−)γ-lycorane (XVII). The hydrochloride, m.p. 255–256° (decomp), was also identical with that of XVII in m.p., mixed m.p. and infra-red spectrum.

Dehydration of β-dihydrocaranine (VIII). To a cooled mixture of phosphorous oxychloride (1 g) and pyridine (3 ml) was added β-dihydrocaranine (350 mg) in portions. After being kept in a refrigerator for 13 hr, the mixture was poured into ice to destroy the excess of phosphorous oxychloride,

basified with 10% Na_2CO_3 and extracted with ether. Concentration of the dried extract afforded crude *β-anhydrodihydrocaranine* (IX, 205 mg) which was dissolved in pet ether and passed through a column of alumina (10 g). 2:1 Pet ether–benzene eluate was crystallized from pet ether to give prisms (130 mg), m.p. 124–126°, $[\alpha]_D^{24}$ −155·3° (*c* 0·13, ethanol), λ_{max} 266, 312 mμ (log ε 4·20, 3·85). (Found: C, 74·91; H, 6·56; N, 5·32. $C_{16}H_{17}O_2N$ requires: C, 75·25; H, 6·71; N, 5·48%).

Hydrogenation of β-anhydrodihydrocaranine (IX) *in ethanol with palladium–carbon*

A mixture of β-anhydrodihydrocaranine (100 mg) and 10% palladium–carbon (100 mg) in ethanol (15 ml) took up 1 mole of hydrogen in 6 hr. Filtration of the catalyst and evaporation of the filtrate gave an oil (85 mg). This was chromatographed in pet ether on alumina (6 g). 3:1 Pet ether–benzene eluate gave (±)*γ-lycorane* (XVIII) (47 mg), $[\alpha]_D^{29°}$ +16·3° (*c* 0·30, ethanol).

The infra-red spectrum was identical with that of (−)γ-lycorane (XVII). *The hydrochloride* had m.p. 255–256° (decomp) and $[\alpha]_D^{22°}$ +13·3° (*c* 0·64, ethanol). (Found: C, 65·11; H, 7·09; N, 4·55. $C_{16}H_{18}O_2N{\cdot}HCl$ requires: C, 65·41; H, 6·86; N, 4·77%).

An aqueous solution of the hydrochloride (3·405 mg) of (−)γ-lycorane (XVII) and that (3·411 mg) of (+)γ-lycorane (XVIII) was basified with aqueous Na_2CO_3 and extracted with pet ether. Concentration of the dried solution gave (±)γ-lycorane (4 mg), which on crystallization from pet ether, formed prisms, m.p. 101–102°, $[\alpha]_D$ 0°, identical with (±)γ-lycorane as obtained below.

Hydrogenation of β-anhydrodihydrocaranine (IX) *with Adams catalyst in acetic acid*

β-Anhydrodihydrocaranine (150 mg) in acetic acid (5 ml) was shaken in hydrogen with Adams catalyst (55 mg) for 5 hr (hydrogen uptake: 13 ml, calc. for 1 H_2: 13 ml). After removal of the catalyst the filtrate was evaporated to dryness *in vacuo*, the residue was dissolved in water, filtered, made alkaline with Na_2CO_3 and extracted with pet ether. The extract was evaporated and the residue (115 mg) chromatographed in pet ether over alumina (4 g). Elution with light petroleum–benzene (5:1, 2:1, and 1:1) gave an oil (51 mg) which was converted into the hydrochloride (20 mg), m.p. 272–273 (decomp), needles (from ethanol), identical with an authentic specimen of (−)β-lycorane hydrochloride in m.p., mixed m.p. and infra-red spectrum. Elution with benzene and benzene–ether (10:1, 5:1) gave (±)*δ-lycorane* (XIX, 35 mg), 125–127, prisms (from light petroleum), $[\alpha]_D^{13°}$ −48·0° (*c* 0·65 ethanol), λ_{max} 291 mμ (log ε 3·68). (Found: 74·74; H, 7·52; N, 5·11. $C_{16}H_{19}O_2N$ requires: C, 74·68; H, 7·44; N, 5·44%).

Hydrogenation of anhydrolycorine (X)

(a) A solution of anhydrolycorine (800 mg) in acetic acid (15 ml) was added to a suspension of reduced platinum oxide (1 g) in acetic acid (15 ml). The mixture was shaken in hydrogen at 60° for 28 hr. The catalyst was removed by filtration, the acetic acid evaporated under reduced press. The residue was dissolved in water, filtered, basified with 10% Na_2CO_3 and extracted with benzene. Concentration of the dried extract gave the product (500 mg) which was chromatographed on alumina (25 g). Elution with pet ether and crystallization of the eluate from the same solvent yielded (±)γ-*lycorane* (200 mg), prisms, m.p. 101–102°, $[\alpha]_D^{24}$ 0° (*c* 0·88 ethanol), λ_{max} 292 mμ (log ε 3·68). The infra-red spectrum was identical with those of (−)γ-lycorane (XVII) and (+)γ-lycorane (XVIII) in carbon disulphide solution. (Found: C, 74·97; H, 7·48; N, 5·45. $C_{16}H_{19}O_2N$ requires: C, 74·68; H, 7·44; N, 5·44%).

The hydrochloride formed needles from water, m.p. 256° (decomp), $[\alpha]_D^{22°}$ 0° (*c* 1·26 ethanol). (Found: C, 65·76; H, 6·89; N, 4·63. $C_{16}H_{18}O_2N{\cdot}HCl$ requires: C, 65·39; H, 5·86; N, 4·77%).

The aqueous layer separated from benzene extract mentioned above was made more basic with 10% NaOH and extracted with benzene. Concentration of the dried extract gave anhydrolycorinone (50 mg). From the alkaline aqueous solution, anhydrolycorinium chloride[3] (100 mg) was isolated through its reineckate.

(b) A solution of anhydrolycorine (250 mg) in ethanol (50 ml) was shaken in hydrogen in the presence of 10% palladium–carbon (250 mg) as catalyst at room temp. The reduction stopped in 28 hr after 2·0 mole equivalents of hydrogen were absorbed. The mixture was worked up in the usual manner to give (±)γ-lycorane (20 mg) and anhydrolycorinone (80 mg).

Hydrogenation of anhydrocaranine (VII) *in ethanol with palladium–carbon*

A solution of anhydrocaranine (200 mg) in ethanol (20 ml) was shaken in hydrogen in the presence of 10% palladium-on-charcoal (250 mg) at 40–45°. After approximately 1 mole equiv. of hydrogen

had been taken up, the reduction stopped in 22 hr. The mixture was worked up in the usual manner and there was obtained (±)γ-lycorane (70 mg), m.p. 101–102°.

Hydrogenation of caranine (XI) *in ethanol with palladium–carbon*

A solution of caranine (300 mg) in ethanol (20 ml) was stirred under hydrogen in the presence of 10% palladium-on-charcoal (300 mg). The reduction stopped in 14 hr after approximately 1 mole of hydrogen had been absorbed. The catalyst was removed by filtration and the ethanol was evaporated. The residue was dissolved in benzene and chromatographed on alumina (20 g). The first eluate with benzene gave (±)γ-lycorane (11 mg). Further elution with 4:1 benzene–ether afforded β-dihydrocaranine (VIII, 145 mg), prisms from ethyl acetate, m.p. 164–168°, identical in m.p., mixed m.p. and infra-red spectrum with an authentic sample.[14]

Further elution with 1:1 benzene–ether gave α-dihydrocaranine (IV, 30 mg), prisms from ethyl acetate, m.p. and mixed m.p. 169–170°.

Modified Oppenauer oxidation of α-dihydrocaranine (IV)

This reaction was carried out independently before the details[4] of a similar reaction has been published by Warnhoff and Wildman. Although the conditions used by us were somewhat different from those employed by the named authors, the product was apparently identical and the yield almost the same as those reported in their paper.

In an atmosphere of nitrogen, metallic potassium (150 mg) was dissolved in t-butyl alcohol (15 ml) which was freshly distilled over metallic sodium. To the solution was added under stirring benzophenone (900 mg) and powdered α-dihydrocaranine (300 mg) and the mixture was refluxed under nitrogen for 3 hr. The colour changed gradually from yellow to yellowish red. The excess of t-butyl alcohol was evaporated under reduced press and the residue extracted with 5% HCl (50 ml) and benzene (20 ml). The benzene layer was extracted twice with 10% HCl (10 ml) and then washed with water (10 ml). The combined aqueous layers were basified with 10% Na_2CO_3 and extracted with benzene (50 ml). Concentration of the dried benzene solution gave a crystalline product (265 mg) which was dissolved in benzene (30 ml) and chromatographed over alumina (10 g). Elution with benzene (180 ml) gave α-dihydrocaranone (XX, 180 mg), which formed needles on recrystallization from ethanol, m.p. 144–146°, $[\alpha]_D^{25°}$ 0° (*c* 1·075, chloroform), $[\alpha]_D^{24°}$ +3·4° (*c* 1·083, ethanol), λ_{max} 290 mμ (log ε 3·66); λ_{max}^{Nujol} 5·87 μ, $\lambda_{max}^{CS_2}$ 5·81 μ (C=O). (Found: C, 71·11; H, 6·54; N, 5·27. Calc. for $C_{16}H_{17}O_3N$: C, 70·83; H, 6·32; N, 5·16%).

Further elution with benzene–ether (1:1) recovered the starting material (IV, 60 mg) unchanged.

The paper chromatography of α-dihydrocaranone by an ascending method using butanol–acetic acid–water (10:1:5) gave one spot (*Rf* 0·58) by Dragendorff's reagent.

Thioketalization of α-dihydrocaranone (XX)

A mixture of α-dihydrocaranone (100 mg), ethanedithiol (0·3 ml) and 47% boron fluoride–etherate (0·3 ml) was kept at room temp for 42 hr. After addition of water (5 ml) and 10% NaOH (4 ml), the mixture was extracted with ether (50 ml) and the ethereal extract washed 5 times with 2 ml portions of 10% NaOH and then with water, concentrated and chromatographed on alumina (5 g). Elution with 1:1 benzene–pet ether afforded a product which was crystallized from ethanol to give *the thioketal* (XXI, 80 mg) as needles, m.p. 131–132°, $[\alpha]_D$ −31·4° (*c* 0·32, chloroform), λ_{max} 294 mμ (log ε 3·68). (Found: C, 62·20; H, 6·22; N, 3·85; S, 17·80. $C_{18}H_{21}O_2NS_2$ requires: C, 62·21; H, 6·09; N, 4·03; S, 18·46%).

Desulphurization of the thioketal (XXI)

A solution of the thioketal (60 mg) in methanol (10 ml) was refluxed with freshly prepared Raney nickel[15] (600 mg) for 6 hr. Filtration from the catalyst and concentration of the filtrate afforded an oil (40 mg) which was converted into its hydrochloride. Crystallization from water gave needles (20 mg),

[14] The author is indebted to Dr. W. C. Wildman of the National Heart Institute, Bethesda, Md. for an authentic sample of β-dihydrocaranine.

[15] *Organic Synthesis*, **21**, 15 (1945).

m.p. 255–256° (decomp), $[\alpha]_D^{26°}$ −14·3° (*c* 0·75, ethanol), identical in m.p., mixed m.p., infra-red spectrum and optical rotation with (−)γ-lycorane hydrochloride. The free base regenerated from the hydrochloride showed the identical infra-red spectrum and optical rotation as those of (−)γ-lycorane (XVII).

Reduction of α-dihydrocaranone (XX)

(a) *With Adams catalyst in acetic acid.* A solution of α-dihydrocaranone (200 mg) in acetic acid (9 ml) was shaken in hydrogen with Adams catalyst (70 mg) for 3 hr. Hydrogen uptake was 21 ml (calc. for 1 H_2: 17 ml). After removal of the catalyst the filtrate was evaporated to dryness and the residue dissolved in water, filtered, basified and extracted with benzene. The dried benzene was evaporated, the residue (190 mg) dissolved in benzene (15 ml) and passed through a column of alumina (10 g). Elution with benzene–ether (10:1) gave crude 1-*epi*-γ-*dihydrocaranine* (XXII, 144 mg) which was recrystallized from a small amount of acetone to give a pure sample (90 mg) as cubes, m.p. 110–111°, $[\alpha]_D^{25°}$ +70·0° (*c* 0·937, ethanol), λ_{max} 291 mμ (log ε 3·68); λ_{max}^{Nujol} 3·02 μ (—OH). (Found: C, 70·50; H, 7·20; N, 5·05. $C_{16}H_{19}O_2N$ requires: C, 70·31; H, 7·01; N, 5·13%).

The acetate prepared with acetic anhydride and pyridine, formed prisms, m.p. 95–96°, (from n-pentane–methanol), $[\alpha]_D^{26°}$ −10·6° (*c* 1·019 ethanol), λ_{max} 291 mμ (log ε 3·58); ν_{max}^{Nujol} 1727, 1269, 1248 cm^{-1} (CH_3COO—). (Found: C, 68·40; H, 6·71; N, 4·46. $C_{18}H_{21}O_4N$ requires: C, 68·55; H, 6·88; N, 4·44%).

The acetate gave 1-epi-γ-dihydrocaranine on hydrolysis.

The eluate with benzene–ether (3:1, 2:1, 1:1) gave crude γ-*dihydrocaranine* (XXIII, 29·0 mg) which on recrystallization with methanol afforded a pure sample (19 mg) as prisms, m.p. 150–151°, $[\alpha]_D^{22°}$ −80·9° (*c* 0·989, ethanol), λ_{max} 291 mμ (log ε 3·65); λ_{max}^{Nujol} 3·08 μ (—OH). (Found: C, 70·55; H, 7·18; N, 4·99. $C_{16}H_{19}O_2N$ requires: C, 70·31; H, 7·01; N, 5·13%).

The acetate formed prisms from n-pentane–methanol, m.p. 85–87°, $[\alpha]_D^{25°}$ −36·6° (*c* 1·134 ethanol), λ_{max} 291 mμ (log ε 3·61); ν_{max}^{Nujol} 1731, 1256, 1238 cm^{-1} (CH_3COO—). (Found: C, 68·27; H, 6·75; N, 4·30. $C_{18}H_{21}O_4N$ requires: C, 68·55; H, 6·88; N, 4·44%).

The acetate gave γ-dihydrocaranine on hydrolysis.

(b) *With lithium aluminium hydride.* To a suspension of lithium aluminium hydride (80 mg) in dry ether (20 ml) was added dropwise under stirring α-dihydrocaranone (150 mg) in dry ether (20 ml) over a period of 20 min, and the mixture refluxed for a further 3 hr. The excess of lithium aluminium hydride was destroyed gradually by addition of water (15 ml), the ethereal layer separated, and the aqueous layer extracted with benzene. The combined organic layers were dried over sodium sulphate and evaporated to dryness under reduced press. The residue (125 mg) was dissolved in benzene and chromatographed over alumina (7 g). Elution with benzene–ether (10:1, 5:1) gave 1-epi-γ-dihydrocaranine (XXII, 65 mg), m.p. and mixed m.p. 110–111°. The eluate with benzene–ether (3:1, 2:1) gave γ-dihydrocaranine (XXIII, 7 mg), identical in m.p., mixed m.p. and infra-red spectrum with an authentic specimen.

(c) *With metallic sodium and ethanol.* To a hot solution of α-dihydrocaranone (118 mg) in dry ethanol (30 ml) was added in portions metallic sodium (1·2 g) over a period of 20 min and the mixture was refluxed under nitrogen for 2 hr. The ethanol was evaporated *in vacuo* in an atmosphere of nitrogen, water (50 ml) was added to the residue, the whole extracted with benzene (150 ml) and the dried extract was evaporated to dryness under reduced press. The residue (89 mg) was dissolved in benzene (10 ml) and chromatographed over alumina (5 g).

Elution with benzene–ether (9:1) gave α-dihydrocaranone (13 mg), m.p. and mixed m.p. 143–145°, The eluate with benzene–ether (3:1) afforded on crystallization from ether γ-dihydrocaranine (XXIII, 27 mg) as prisms, m.p. and mixed m.p. 150–151°.

Reaction of γ-dihydrocaranine (XXIII) *with thionyl chloride*

A solution of γ-dihydrocaranine (88 mg) in thionyl chloride (4 ml) was allowed to stand overnight. The excess of thionyl chloride was completely removed and ice-cold water was added. The mixture was filtered, basified with Na_2CO_3 and extracted with pet ether. The dried extract was evaporated and the residue gave on twice recrystallization from ethanol *a chloro-compound* (XXIV, 46 mg) as needles, m.p. 140–141°, $[\alpha]_D^{21°}$ +38·4° (*c* 0·628, chloroform), λ_{max} 291 mμ (log ε 3·54). The infra-red spectrum did not show a band corresponding to the hydroxyl group and Beilstein test was positive. (Found: C, 65·87; H, 6·29; N, 4·95. $C_{16}H_{18}O_2NCl$ requires: C, 65·85; H, 6·22; N, 4·80%).

Hydrogenation of a chloro-compound (XXIV) *with Adams catalyst in ethanol*

A solution of a chloro-compound (20 mg) in ethanol (3 ml) was shaken in hydrogen for 3 hr. Hydrogen uptake was 1·6 ml (calcd. for 1 H_2: 1·52 ml). After removal of the catalyst the ethanol was evaporated to dryness under reduced press and the residue dissolved with dil HCl, filtered, basified with Na_2CO_3 and extracted with pet ether. The dried extract was evaporated to dryness and the residue (13 mg) chromatographed over alumina (1 g). Elution with benzene–pet ether (10:1) gave an oil (9 mg), identical in infra-red spectrum and optical rotation with (−)γ-lycorane (XVII).

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NATURAL FURAN DERIVATIVES—VII[1]

THE PRESENCE OF A SEVEN-MEMBERED α,β-UNSATURATED LACTONE IN OBACUNONE

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Abstract—Oxidation of obacunone with potassium permanganate afforded three neutral substances containing a furan ring; a glycol, $C_{26}H_{32}O_9$, a hydroxy-dilactone, $C_{25}H_{30}O_8$, and a dilactone, $C_{24}H_{28}O_7$. Obacunoic acid was isomerized to iso-obacunoic acid. From these experimental results and from various reactions of etio-obacunoic acid, the presence of a seven-membered, α,β-unsaturated lactone system (Ia) in obacunone was indicated.

IN Part V of this series,[2] it was shown that three double bonds, in the furan ring and α,β-unsaturated lactone, are present in obacunone. The unsaturated lactone of obacunone can be oxidized under mild condition, without affecting the furan ring. Oxidation of obacunone (I) with potassium permanganate in a mixture (9:1) of acetone and water affords three neutral substances; a glycol (II), $C_{26}H_{32}O_9$, a hydroxy-dilactone* (III), $C_{25}H_{30}O_8$, and a dilactone (IV), $C_{24}H_{28}O_7$. These three substances show absorptions of a furan ring at 3·20 and 11·44 μ in their infra-red spectra and show that they all retain the furan ring.

Treatment of the glycol (II) with acetic anhydride and pyridine affords a diacetate (no absorption of a hydroxyl group in its infra-red spectrum) while its oxidation with lead tetra-acetate or periodic acid results in consumption of one equivalent of the oxidant, which shows that the double bond in the α,β-unsaturated lactone of obacunone had been oxidized into a vicinal glycol. Further oxidation of the glycol (II) with potassium permanganate gives IV.

The hydroxy-dilactone (III) forms a monoacetate (no absorption of hydroxyl group in its infra-red spectrum) and a mono-2,4-dinitrophenyl-hydrazone. Alkaline hydrolysis of III results in consumption of two equivalents of alkali and acidification of the hydrolysate regenerates III. Presence of one hydroxyl, two six-membered lactones, and one carbonyl in the hydroxy-dilactone is borne out, besides the above experimental results, by the presence of absorptions at 2·98, 5·73 and 5·80 μ in its infra-red spectrum.

The dilactone (IV) consumes two equivalents of alkali in alkaline hydrolysis and is recovered on acidification of its hydrolysate. The infra-red spectrum of IV with absorptions at 5·67, 5·77 and 5·87 μ indicates the presence of a newly formed γ-lactone, δ-lactone originally present in obacunone, and a ketone. This ketone has a

* This substance was designated to "substance A" in Part VI.[3]

[1] Part VI: T. Kubota, T. Matsuura, T. Kamikawa and T. Tokoroyama, *Tetrahedron Letters* No. 8, 1 (1960).

[2] T. Tokoroyama, T. Kamikawa and T. Kubota, *Bull. Chem. Soc. Japan* **34**, 131 (1961).

poor reactivity and does not form an oxime or a semicarbazone under conditions identical with that used for obacunone.

The α,β-unsaturated lactone in obacunone undergoes irreversible fission of the ring by the action of alkali and forms obacunoic acid (V).[3–5] This acid (V) somewhat resists permanganate oxidation but oxidation under drastic condition affords the foregoing dilactone (IV). Obacunoic acid has an absorption maximum at 210 mμ (ε 11,600) in its ultra-violet spectrum. As indicated in Table 1, this absorption is an overlapped maxima of the furan ring and α,β-unsaturated carboxylic acid. The

TABLE 1

	λ_{max}	ε
Obacunoic acid	210	11,600
Marrubiin[7]	208	5,600
	212	5,600
	216	5,000
Limonin[8]	208	6,300
Iso-obacunoic acid	210	6,600

absorption maximum of 210 mμ suggests that obacunoic acid is a β-monosubstituted α,β-unsaturated acid.[6]

The hydroxyl group in obacunoic acid resists oxidation with chromium trioxide under various conditions and is therefore considered to be tertiary. By heating obacunoic acid with acetic anhydride and sodium acetate, Kaku and Li[3] obtained an acid of m.p. 154–156°, and Emerson[4] isolated an acid of m.p. 145°. The latter acid was recognized from its analytical values to be acetyl-obacunoic acid. Re-examination of this reaction afforded an acid (VI) of m.p. 154–155°, an isomer of obacunoic acid, and was named iso-obacunoic acid. Infra-red spectrum of iso-obacunoic acid lacks the absorption of a double bond conjugated with the carboxyl at 6·16 μ, present in obacunoic acid, and that of hydroxyl. Its ultra-violet spectrum indicates only the absorption of a furan ring (Table 1).

Iso-obacunoic acid is also obtained by hydrolysis of the amorphous methyl ester obtained by application of diazomethane to obacunoic acid or its methyl ester for a long period of time. It is also obtained by long heating of obacunone or obacunoic acid with alkali.*

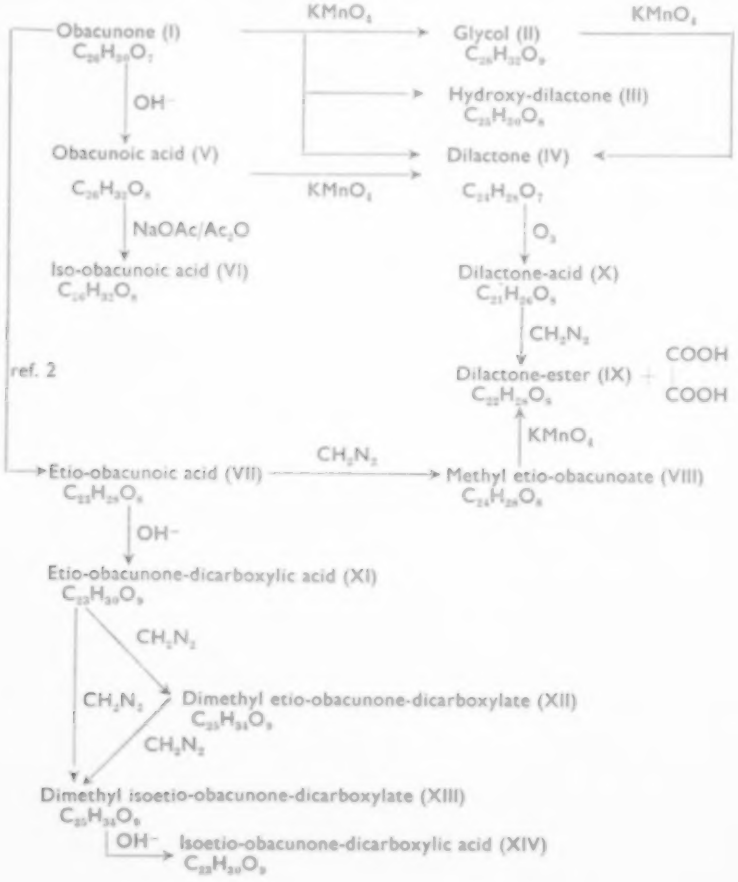
The oxidative degradation of obacunone and formation of iso-obacunoic acid can be explained, as shown below, by considering the presence of a seven-membered unsaturated lactone grouping (Ia) in obacunone (I). Partial structures IIa, IIIa, IVa, Va, and VIa will therefore be given respectively for the glycol (II), hydroxy-dilactone (III), dilactone (IV), obacunoic acid (V), and iso-obacunoic acid (VI).

The presence of a seven-membered α,β-unsaturated lactone (Ia) is also supported from various reactions of etio-obacunoic acid[2] (VII), $C_{23}H_{28}O_8$, obtained by degradation of the furan ring in obacunone. Oxidation of methyl etio-obacunoate[2] (VIII) with potassium permanganate in boiling acetone affords oxalic acid and a dilactone

* Reaction of obacunone with alkali will be reported in a forthcoming paper.

[3] T. Kaku and P. Li, *J. Pharm. Soc. Japan* **55**, 1153 (1935).
[4] O. L. Emerson, *J. Amer. Chem. Soc.* **70**, 545 (1948); **73**, 2621 (1951).
[5] F. M. Dean and T. A. Geissman, *J. Org. Chem.* **23**, 596 (1958).
[6] A. T. Nielsen, *J. Org. Chem.* **22**, 1539 (1957).
[7] W. Cocker, B. E. Cross, S. R. Duff, J. T. Edward and T. F. Holley, *J. Chem. Soc.* 2540 (1953).
[8] T. Tokoroyama, *J. Chem. Soc. Japan* **79**, 316 (1958).

ester (IX), $C_{22}H_{28}O_8$, as the main products. Infra-red spectrum of IX shows absorptions at 5·68 (γ-lactone) and 5·75 μ(δ-lactone and ester). The ester (IX) was identical with the dilactone ester obtained by methylation of dilactone acid (X), $C_{21}H_{26}O_8$.



which was formed by ozonolysis of the dilactone (IV). This indicates the presence of Ia grouping in etio-obacunoic acid (VII) and IVa grouping in the dilactone ester (IX).

Etio-obacunone-dicarboxylic acid (XI),[2] $C_{23}H_{30}O_9$, obtained by mild alkaline hydrolysis of etio-obacunoic acid, and its dimethyl ester (XII), when allowed to stand with diazomethane over a long period time, form a dimethyl ester (XIII), $C_{25}H_{34}O_9$, named dimethyl isoetio-obacunone-dicarboxylate, which no longer exhibits infra-red absorptions of a hydroxyl group and of double bond conjugated to carboxyl group and can be hydrolysed to isoetio-obacunone-dicarboxylic acid (XIV), $C_{23}H_{30}O_9$. This indicates the presence of VIa grouping in isoetio-obacunone-dicarboxylic acid (XIV), as in iso-obacunoic acid (VI).

The glycol (II) is recovered on alkaline hydrolysis followed by acidification of its hydrolysate. This abnormal reaction in which the seven-membered saturated lactone ring undergoes reversible ring fission is rather interesting. Such stability of this lactone ring, in spite of the irreversible fission of saturated seven-membered lactone ring in other compounds of obacunone series,* is probably due to the fact that the two vicinal hydroxyl groups take the conformation by which they easily undergo relactonization by the steric effect of other groups in the molecule.

EXPERIMENTAL

Permanganate oxidation of obacunone (I)

Obacunone (10 g) was dissolved in a mixture of acetone and water (9:1, 250 ml) and powdered potassium permanganate (5·6 g, 3 atom equivalents) added all at once under stirring and ice-cooling. The mixture was stirred at 20° until the permanganate was completely consumed. Manganese dioxide precipitated was filtered and washed with hot acetone 3 times. The filtrate and washing were combined and evaporated to a small volume under reduced press. Dilution with water precipitated a crystalline mass, which on digestion with chloroform was separated into the soluble part (A) and the insoluble part (B). The above aqueous filtrate was shaken with chloroform to remove the neutral material which was combined with (A). Acidification of the aqueous layer gave precipitates (C) which were filtered and dried (6·4 g).

Dilactone (IV). The soluble part (A) was washed with water, dried with anhydrous sodium sulphate and evaporated under reduced pressure. The residue (1·3 g) was dissolved in chloroform and passed through a column containing silicagel (39 g). Elution with chloroform–acetone (9:1) gave a crystalline solid which was recrystallized from acetone–water as leaflets or long prisms (484 mg), m.p. 282–284° (dec). $[\alpha]_D^{11^0}$ −39·3° (*c*, 0·981 in chloroform). I.R. spectrum (Nujol): 3·20 (furan), 5·67 (γ-lactone), 5·77 (δ-lactone), 5·84 (ketone), 11·44 μ (furan). λ_{max}^{EtOH} 208·5 mμ (ε 6,400). Saponification equivalent: 209. Calc. for two lactones: 214. (Found: C, 67·24; H, 6·59. Calc. for $C_{24}H_{28}O_7$: C, 67·27; H, 6·59%.)

Glycol (II). Recrystallizations of the insoluble part (B) from acetone–water gave prisms (1·2 g), m.p. 233° (dec). I.R. spectrum (Nujol): 2·91 and 2·97 (hydroxyl), 3·18 (furan), 5·77 (lactones and ketone), 11·44 μ (furan). (Found: C, 61·61; H, 6·87. Calc. for $C_{26}H_{32}O_9 \cdot H_2O$: C, 61·65; H, 6·77 %.) On titration with lead tetra-acetate and periodic acid, the glycol consumed respectively 0·9 and 0·8–1·0 mole of the reagent.

Hydroxy-dilactone (III). The precipitates (C) were recrystallized from methanol–ether as silky needles, m.p. 289–291° (dec). From the mother liquor separated dimorphic plates, m.p. 289–291° (dec), which could be converted to the original needles on recrystallization from methanol–ether. IR spectrum (nujol): 2·98 (hydroxyl), 5·73 (shoulder; lactones), 5·80 (ketone), 11·44 μ (furan). Saponification equivalent: 223. Calc. for two lactones: 229. (Found: C, 65·73; H, 6·61. Calc. for $C_{25}H_{30}O_8$: C, 65·49; H, 6·60%.)

* Behaviour of the lactone ring in compounds with saturated seven-membered lactone derived from obacunone will be discussed in the following paper.

Diacetate of the glycol (II)

The glycol was acetylated with acetic anhydride and pyridine at room temp overnight. Recrystallization of the product from ethanol gave prisms, m.p. 247–248° (dec). I.R. spectrum (Nujol): 3·18 (furan), 5·77 (acetoxyls and lactones), 5·88 (ketone), 11·44 μ (furan). Acetyl number: 1·87. (Found: C, 63·02; H, 6·87. Calc. for $C_{30}H_{36}O_{11}$: C, 62·91; H, 6·34%.) The diacetate gave the parent glycol (II) on alkaline hydrolysis followed by acidification.

2,4-*Dinitrophenylhydrazine of the hydroxy-dilactone* (III)

The 2,4-dinitrophenylhydrazone prepared in the usual manner, was recrystallized from a mixture of ethyl acetate, ethanol and water as yellow needles, m.p. 294° (dec). (Found: C, 58·14; H, 5·25; N, 8·87. Calc. for $C_{31}H_{34}O_{11}N_4$: C, 58·29; H, 5·25; N, 8·77%.)

Monoacetate of the hydroxy-dilactone (III)

The hydroxy-dilactone was acetylated with acetic anhydride and pyridine at room temp overnight. Recrystallization of the product from acetone gave prisms, m.p. 304–305° (dec). I.R. spectrum (Nujol): 5·73 (acetoxyl and lactones), 5·83 (ketone). Acetyl number: 0·97. (Found: 64·84; H, 6·40. Calc. for $C_{32}H_{32}O_9$: C, 64·79; H, 6·44%.) The monoacetate gave the parent hydroxy-dilactone (III) on alkaline hydrolysis followed by acidification.

Permanganate oxidation of the glycol (II)

To a stirred solution of the glycol (1 g) in acetone (80 ml) was added powdered potassium permanganate (0·8 g) and after standing overnight, water (10 ml) was added. The mixture was treated as described in the permanganate oxidation of obacunone and divided into the 3 fractions: chloroform-soluble fraction (A), chloroform-insoluble fraction (B) and water-soluble fraction (C). The fraction (A) was evaporated and the residue (247 mg) chromatographed through a column containing silica gel (9 g). Elution with chloroform–acetone (9:1) gave crystalline mass which was recrystallized from acetone–water as leaflets (40 mg), m.p. 282–284° (dec), pure and mixed with dilactone (IV). The infra-red spectrum was identical with that of the dilactone (IV).

The fraction (B) was recrystallized from acetone–water as prisms (61 mg), m.p. 233° (dec), pure and mixed with the glycol (II).

The fraction (C) was acidified and the resulting precipitates (397 mg) were recrystallized from dilute methanol. Only a minute amount of plates, m.p. 263° (dec), was obtained, which was not further investigated.

Lead tetra-acetate oxidation of the glycol (II)

To a stirred solution of the glycol (500 mg) in glacial acetic acid (20 ml) was added a solution of lead tetra-acetate (400 mg) in glacial acetic acid (5 ml). After the mixture was heated at 60° for 1 hr, the solvent was removed under reduced press. The residue was dissolved in ethanol and mixed with a solution of 2,4-dinitrophenylhydrazine in ethanol containing sulphuric acid. Recrystallization of the precipitates from a mixture of ethyl acetate, ethanol and water gave yellow needles, m.p. 255° (dec). I.R. spectrum (Nujol): 5·76, 5·83, 5·88, 6·20, 6·34 μ. (Found: C, 57·46; H, 5·03; N, 8·43. Calc. for $C_{32}H_{34}O_{12}N_4$: C, 57·64; H, 5·14; N, 8·40%.)

Obacunoic acid (V)

Obacunoic acid was prepared according to the method of Kaku and Li[3] and recrystallized from acetone–water and then from ethanol as needles, m.p. 214–215°. I.R. spectrum (Nujol): 2·98 (hydroxyl), 3·6–4·0 (carboxylic acid), 5·72 (δ-lactone), 5·88 (ketone and α,β-unsaturated carboxylic acid), 6·16 (conjugated double bond), 11·45 μ (furan). λ_{max}^{EtOH} 210 mμ (ε 11,600).

Methyl obacunoate

Methyl obacunoate was prepared by a slight modification of the method of Kaku and Li[3]. Excess of diazomethane, soon after the addition, should be removed by evaporation under reduced pressure or by decomposition with the addition of acetic acid, in order to obtain the methyl ester in high yield. Recrystallization from ethanol gave plates, m.p. 175–176°. I.R. spectrum (nujol): 5·78 (δ-lactone), 5·84 (ketone and α,β-unsaturated ester), 6·17 μ (conjugated double bond).

Iso-obacunoic acid (VI)

(a) Obacunoic acid (1 g) and anhydrous sodium acetate (1 g) was refluxed in acetic anhydride (30 ml) for 1 hr, according to the method of Kaku and Li[8]. After cooling the mixture was poured into ice-water and allowed to stand overnight. The viscous material solidified on scatching was filtered and treated with benzene. The benzene insoluble solid was filtered and recrystallized from chloroform–benzene as fine needles (400 mg), m.p. 155–157°. I.R. spectrum (Nujol): 3·18 (furan), 3·6–4·0 (carboxylic acid), 5·77 (δ-lactone), 5·84 (carboxylic acid), 5·89 μ (ketone). λ_{max}^{EtOH} 210 mμ (ε 6,600). Saponification equivalent: 241. Calc. for monobasic acid lactone: 236. (Found: C, 65·86; H, 6·78. Calc. for $C_{26}H_{32}O_8$: C, 66·08; H, 6·8%.)

(b) Obacunoic acid dissolved in acetone was mixed with an ether solution of a large excess of diazomethane, and the mixture allowed to stand for 2 days. Evaporation of the solvent left an amorphous solid which failed to crystallize. The amorphous methyl ester was hydrolysed with 1 N NaOH on the water-bath. Acidification with dil HCl gave a solid which recrystallized from chloroform–benzene as fine needles, m.p. 150–152°, pure and mixed with an authentic sample of iso-obacunoic acid.

Permanganate oxidation of obacunoic acid (V)

To a solution of obacunoic acid (2 g) in acetone (100 ml), was added in portions under refluxing powdered potassium permanganate (4 g). After refluxing for 1 hr the mixture was cooled and acidified with dil HCl, and manganese dioxide decomposed with sulphur dioxide. The clear solution was evaporated under reduced press and the crystals separated were filtered and treated with chloroform. Recrystallization of the chloroform-insoluble crystals from acetone–water gave needles (1·1 g), m.p. 197–198°, pure and mixed with an authentic sample of obacunoic acid. The chloroform-soluble part was evaporated and the residue recrystallized from acetone–water as leaflets (97 mg), m.p. 278–279° (dec), pure and mixed with an authentic sample of dilactone (IV). The infra-red spectrum was identical with that of the dilactone (IV).

Attempted oxidation of the hydroxyl group of obacunoic acid

(a) *With chromium trioxide-pyridine.* A solution of obacunoic acid (1 g) in pyridine (20 ml) was added to a mixture of chromium trioxide (0·6 g) in pyridine (6 g) below 20°, and the mixture allowed to stand at room temp overnight. The reaction mixture was diluted with water (50 ml) and extracted with chloroform. The chloroform layer was washed with dil HCl and then with water, dried and evaporated. Recrystallization of the residue from ethanol gave needles (439 mg), m.p. 204–206° (dec), pure and mixed an authentic sample of obacunoic acid. The infra-red spectrum was identical with that of obacunoic acid.

(b) *With chromium trioxide–acetone–sulphuric acid.* To a solution of obacunoic acid (236 mg) in acetone (12 ml) was added 1·38 ml of chromium trioxide solution, prepared from chromium trioxide (270 mg), sulphuric acid (0·3 ml) and water (9·7 ml), under ice-cooling. After 4 hr standing, the mixture was diluted with water. Resulting precipitates were filtered and recrystallized from acetone–water to give obacunoic acid (200 mg), m.p. 206–207°.

Ozonolysis of the dilactone (IV)

Ozonized oxygen was passed through a solution of the dilactone (1·5 g) in methylene chloride (70 ml) for 3 hr under ice-cooling. The opaque solution was poured into a large volume of water. After standing at room temp for 2 days, the organic layer was separated, dried and evaporated. The residue was dissolved in chloroform and shaken with aqueous sodium bicarbonate solution. The bicarbonate solution was acidified with dil HCl and extracted with ether. Evaporation of the ether solution left the dilactone-acid as a gum which did not crystallize in this stage. The crude dilactone-acid (X) was dissolved in acetone and methylated with an excess of diazomethane in ether. The dilactone-ester (IX) was recrystallized from methanol as needles (280 mg), m.p. 219–221°. I.R. spectrum (Nujol): 5·68 (γ-lactone), 5·75 (δ-lactone and ester), 5·84 μ (ketone). (Found: C, 62·60; H, 6·72. Calc. for $C_{32}H_{28}O_8$: C, 62·84; H, 6·71%.)

This methyl ester was hydrolysed with 1 N KOH below 80° for 1 hr. Acidification with 1 N HCl separated crystals which on recrystallization from acetone–water gave the dilactone-acid as needles, bubbled at 158°, then solidified and melted at 267–268°. I.R. spectrum (Nujol): 5·72–5·77, 5·84, 5·89 μ. (Found: C, 61·22; H, 6·48. Calc. for $C_{31}H_{28}O_8 \cdot \frac{1}{2}H_2O$: C, 60·72; H, 6·55%.)

Permanganate oxidation of methyl etio-obacunoate (VIII)*

To a boiling solution of methyl etio-obacunoate (2 g) in acetone (50 ml) was added in portions powdered potassium permanganate (4·5 g). The mixture was refluxed until the permanganate was consumed completely. Manganese dioxide was filtered and washed with hot acetone 3 times. The filtrate and washings were combined and evaporated to a small volume under reduced pressure and then shaken with a mixture of chloroform and dil HCl. The chloroform layer was shaken with aqueous sodium bicarbonate solution.

The chloroform layer was washed with water, dried and evaporated. Recrystallization of the residue from acetone–water gave needles (250 mg), m.p. 218–220°, which were identified as the dilactone-ester (IX) by mixed m.p. and infra-red spectrum.

The bicarbonate solution was acidified with dil HCl. The resulting precipitates were filtered, dried and recrystallized from acetone–water as prisms (50 mg), m.p. 254–255°. I.R. spectrum (Nujol): 2·89, 5·69, 5·80–5·84 μ. (Found: C, 61·45; H, 6·86. Calc. for $C_{31}H_{48}O_8$: C, 61·75; 6·19%.) This compound was not further investigated.

The above filtrate was continuously extracted with ether. Evaporation of the ether solution left needles (700 mg), m.p. 95–101°, which recrystallized from water as prisms, m.p. 101–104°, pure and mixed with an authentic sample of oxalic acid dihydrate.

Dimethyl isoetio-obacunone-dicarboxylate (XIII)

To a solution of etio-obacunone-dicarboxylic acid (XI)[2] in methanol was added an excess of diazomethane in ether solution and the mixture allowed to stand for a day in refrigerator. After evaporation of the solvent, the residue was recrystallized from methanol–water as prisms, m.p. 179–180°. I.R. spectrum (Nujol): 5·70, 5·74, 5·88 μ. Ultra-violet spectrum: λ_{204}^{EtOH} ε 890, λ_{219}^{EtOH} ε 560. (Found: C, 62·73; H, 7·31. Calc. for $C_{33}H_{54}O_8$: C, 62·75; H, 7·16%.)

Isoetio-obacunone-dicarboxylic acid (XIV).

Dimethyl isoetio-obacunone-dicarboxylate (0·5 g) was heated with 1 N NaOH (10 ml) at 80° for 1 hr. After cooling, the mixture was acidified with dil HCl (congo red) and allowed to stand overnight. Separated crystals (450 mg), m.p. 167–169° (dec) were recrystallized from acetone–water as prisms, m.p. 167–169° (dec). I.R. spectrum (Nujol): 2·83, 2·97, 5·73, 5·88 μ. Saponification equivalent: 159. Calc. for lactone dicarboxylic acid: 153. (Found: C, 60·02; H, 6·81. Calc. for $C_{29}H_{44}O_9 \cdot \frac{1}{2}H_2O$: C, 60·10; H, 6·80%.)

This acid, by the methylation with diazomethane, could be converted to the dimethyl ester (XII), m.p. 184–184·5°, whose infra-red spectrum was identical with that of the above dimethyl ester, m.p. 179–180°.

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NATURAL FURAN DERIVATIVES—VIII[1]

RELATIONSHIP BETWEEN THE FURAN RING AND SIX AND SEVEN-MEMBERED LACTONE RINGS IN OBACUNONE

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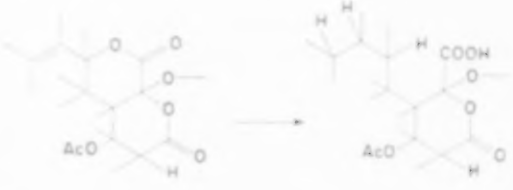
Abstract—The presence of a α,β-epoxy-(β-furyl)-δ-lactone group in obacunone was suggested, from the catalytic reduction and conversion to desoxy compound of the dilactone (V), one of the oxidation products of obacunone with potassium permanganate. The stability of saturated, seven-membered lactone ring in obacunone derivatives was discussed. Degradation of the masked hydroxyl group is tertiary and is bonded to isopropyl group. Formula Ie was proposed for the partial structure of obacunone.

In the preceding paper of this series,[1] two of the authors (T. Ka. and T. Ku.) indicated the presence of an α,β-unsaturated, seven-membered lactone group (Ia) in obacunone.

Ia

Obacunone possesses another lactone, which is known to be a six-membered lactone from its infra-red absorption and its facile relactonization.[2] Dean and Geissman[2] obtained methyl hydrogen octahydro-obacunoninate (II) by catalytic reduction of obacunone (I) followed by treatment with methanol. These workers also obtained



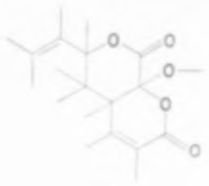
III IV

hexahydronomilinic acid (IV) by catalytic reduction of nomilin* (III). From extremely low values of p*Ka* of these two acids, presence of an oxide linkage was

* Nomilin was found to be an acetoxy-dihydro-obacunone, a compound with an acetoxyl group in β-position of the α,β-unsaturated lactone in obacuhone.[2,3]

[1] Part VII: T. Kamikawa and T. Kubota, *Tetrahedron* **12**, 262 (1961).
[2] F. M. Dean and T. A. Geissman, *J. Org. Chem.* **23**, 596 (1958).
[3] O. H. Emerson, *J. Amer. Chem. Soc.* **73**, 2621 (1951).

assumed in the α-position of the carbonyl group in the six-membered lactone of obacunone and nomilin which undergoes hydrogenolysis. The conversion of III to IV was explained by assuming the following partial structural formulae.*



Ib

The dilactone[1] (V), $C_{24}H_{28}O_7$, one of the permanganate oxidation products of obacunone, retains the furan ring and six-membered lactone present in obacunone, and possesses a five-membered lactone ring newly formed by oxidation of the unsaturated, seven-membered lactone. Catalytic reduction of V results in saturation of the

Ic

furan ring to give two products, a tetrahydro-dilactone (VI), $C_{24}H_{32}O_7$, and a monocarboxylic acid (VII), $C_{24}H_{34}O_7$. Infra-red spectra of VII (5·69 and 5·90 μ) and its methyl ester (5·70 μ) indicate the presence of a five-membered lactone in VII and this fact shows that the six-membered lactone in V had suffered hydrogenolysis by activation by the double bond† of the furan ring (β-furyl group[4]). Since the p*Ka* value of the acid (VII) is of a low order (Table 1), comparable to that of methyl hydrogen octahydro-obacunoninate (II), presence of an oxide linkage in the α-position of carboxyl group may be considered. Consequently, partial formula Ic would be given to the six-membered lactone in obacunone and the dilactone (V). This partial structure is also supported by the low p*Ka* value (indicates an oxygen linkage in α-position of the carboxyl group) of etio-obacunoic acid[5] (VIII), obtained by degradation of the furan ring in obacunone.

Treatment of the dilactone (V) with hydriodic acid gives desoxydilactone (IX), $C_{24}H_{28}O_6$, whose ultra-violet spectrum shows absorption maximum at 214 mμ (ε 12,300). The difference curve with the absorption curve of the dilactone (V) (λ_{max} 208 mμ, ε 6140) shows absorption maximum at 218 mμ (ε 7200). This nature of ultra-violet absorption spectrum agrees well with that of the ultra-violet spectra of

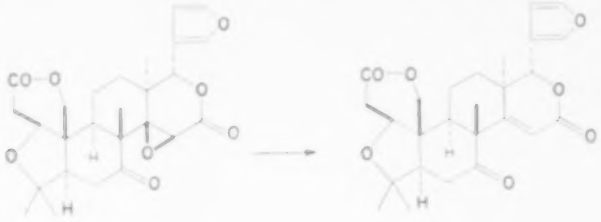
* These formulae suggest that obacunone would be represented by the formula Ib. Dean and Geissman stated that the double bond in III may be a part of the furan ring.

† Since obacunone has no double bond other than those in the furan ring and unsaturated lactone,[5] the double bonds in the dilactone (V) are only two in the furan ring.

[4] T. Kubota and T. Tokoroyama, *Chem. & Ind.* 1298 (1957). Also see T. Tokoroyama, *J. Chem. Soc. Japan* **79**, 319 (1958).

[5] T. Tokoroyama, T. Kamikawa and T. Kubota, *Bull. Chem. Soc. Japan* **34**, 131 (1961).

limonin (X) and desoxy-limonin[6] (XI), formed by treatment of limonin with hydriodic acid. Formulae X and XI have been given for limonin and desoxy-limonin by Arigoni and others,[7] and it is concluded that an α,β-epoxy-δ-lactone group adjacent to the furan ring, as indicated by the formula V, is present in the dilactone.



X XI

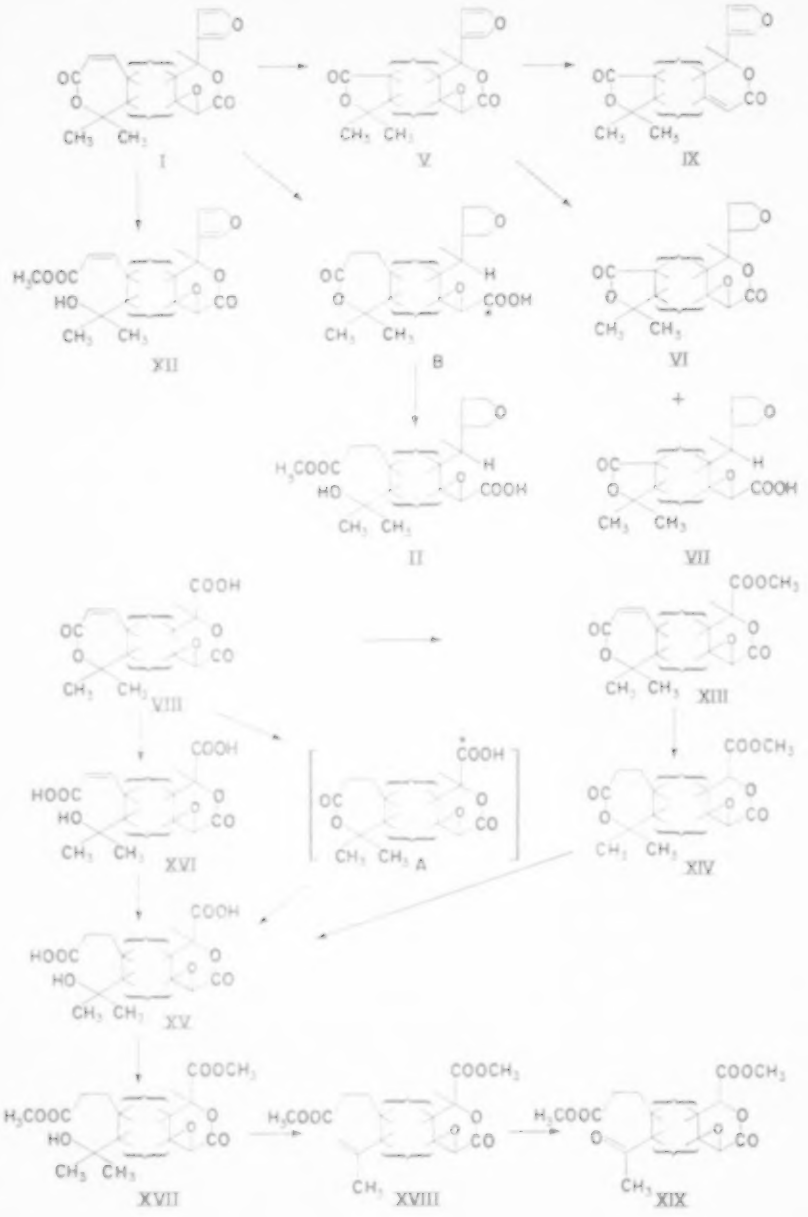
Methyl hydrogen octahydro-obacunoninate (II), obtained by catalytic reduction of obacunone (I) followed by treatment with methanol, is also obtained by catalytic reduction of methyl obacunoate (XII).[2] This substance (II) is now formulated as $C_{27}H_{42}O_8$. This fact can be interpreted as hydrogenolysis of the six-membered lactone due to activation by the furan ring, in the first case, but the latter involves, in addition to the hydrogenolysis, methanolysis of the saturated seven-membered lactone. This instabilization of the saturated, seven-membered lactone is also observed in the reduction of compounds of etio-obacunoic acid series to be described below.

Catalytic reduction of methyl etio-obacunoate (XIII) merely gives methyl dihydro-etio-obacunoate (XIV),[5] but that of etio-obacunoic acid (VIII) itself results in absorption of one mole of hydrogen and recrystallization of the product from acetone–water mixture gives a saturated hydroxy-dicarboxylic acid (XV), $C_{23}H_{32}O_9$, named dihydro-etio-obacunone-dicarboxylic acid. This acid (XV) possesses one hydroxyl group which resists acetylation and is titrated as a dicarboxylic acid lactone by alkali. The acid (XV) can be derived from etio-obacunoic acid by two different routes. The one is the catalytic reduction of etio-obacunone-dicarboxylic acid (XVI),[5] obtained by a mild saponification of etio-obacunoic acid, and the other is alkaline hydrolysis of methyl dihydroetio-obacunoate (XIV). Therefore, it is clear that XV was formed by hydrolysis of the seven-membered lactone ring in the dilactone acid (formula A) during recrystallization, formed as intermediate during reduction of etio-obacunoic acid (VIII). It is interesting that the saturated, seven-membered lactone has undergone hydrolysis in the case of the intermediate A, while methyl dihydroetio-obacunoate (XIV) can be recrystallized from acetone–water without hydrolysis of the lactone ring. In the formation of XV and II, the saturated, seven-membered lactone of the precursors, A and B, probably suffers hydrolysis or methanolysis to give XV and II by catalytic action of the carboxyl group (marked *) with a strong acidity. Naturally, compounds (for example, XIV) which do not have such a strong acid group in their molecule undergo irreversible ring fission by alkaline hydrolysis.*

* There is an exception of a reversible ring-fission of the saturated, seven-membered lactone in the glycol, $C_{26}H_{32}O_9$, one of the products of permanganate oxidation of obacunone.[1]

[6] T. A. Geissman and V. Tulagin, *J. Org. Chem.* **11**, 760 (1946).

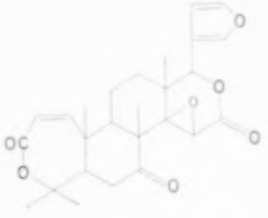
[7] D. Arigoni, D. H. R. Barton, E. J. Corey, O. Jeger, L. Caglioti, Sukh Dev, P. G. Ferrini, E. R. Glazier, A. Melera, S. K. Pradhan, K. Schaffner, S. Sternhell, J. F. Templeton and S. Tobinaga, *Experientia* **16**, 41 (1960).



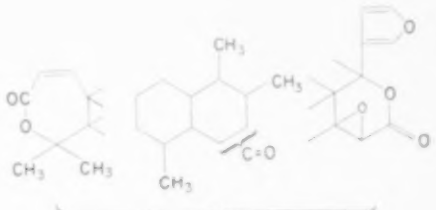
The tertiary nature of the masked hydroxyl group in the unsaturated, seven-membered lactone in obacunone was assumed from the resistance of obacunoic acid to oxidation by chromium trioxide.[1] The methyl ester (XVII) of dihydroetio-obacunone-dicarboxylic acid (XV) is not acetylated by treatment with acetic anhydride and pyridine at room temperature but is easily dehydrated by treatment with acetic anhydride and potassium hydrogen sulphate or with phosphoryl chloride and pyridine

to form an anhydro-compound (XVIII), $C_{25}H_{34}O_8$, which shows absorption of terminal methylene at 11·23 μ in its infra-red spectrum and forms formaldehyde and a norketone (XIX), $C_{24}H_{32}O_9$, by ozonolysis.* The norketone is positive to the iodoform reaction, indicating that a methyl ketone group had newly been formed. From these experimental results, it may be concluded that the masked hydroxyl group in the unsaturated, seven-membered lactone in obacunone is tertiary and is bonded to iso-propyl group.

There are no experimental evidences to show that the two lactone rings in obacunone are directly bonded through common carbon atoms (cf. formula Ib), as assumed by Dean and Geissman.[2] It seems more appropriate to assumed, therefore, that the two lactone groups are present separately in the obacunone molecule, as indicated in the formula I



I d



I e

Lithium aluminium hydride reduction of methyl etio-obacunoate (XIII) and dehydrogenation of its amorphous product with selenium affords 1,2,5-trimethylnaphthalene. This seems to suggest that the two carbocyclic rings in obacunone are present as hydronaphthalene. Recently, Arigoni and others[7] proposed the formula Id as the plausible and biogenetically attractive one for obacunone by deduction from the structure X of limonin, which is considered to be closely related to obacunone.

From the experimental results obtained to date, partial structure of Ie is presented for obacunone.

TABLE 1. p*Ka* VALUES

	In dimethylformamide–H_2O (1:1)	In H_2O
Acetic acid	6·52	—
Benzoic acid	6·12	—
Obacunoic acid	6·15	—
Acid (VII)	4·90	—
Methyl hydrogen octahydro-obacunoninate (II)	4·46	2·9[8]
Hexahydrolimonic acid	—	2·7[9]
Etioobacunoic acid (VIII)	4·90	—

* In a communication,[5] formation of acetone and a compound of $C_{22}H_{28}O_9$ was reported but it was later found that acetone had been derived from impurities in a solvent and the latter compound was due to erroneous analytical calculation.

[8] T. Kubota, T. Kamikawa, T. Tokoroyama and T. Matsuura, *Tetrahedron Letters* No. 8, 1 (1960).
[9] A. Melera, K. Schaffner, D. Arigoni and O. Jeger, *Helv. Chim. Acta* **40**, 1420 (1957).

EXPERIMENTAL

Measurement of p*Ka values*. The p*Ka* values of compounds listed in Table 1 were measured in dimethylformamide–water (1:1), according to the method of Parke and Davis.[10]

Methyl hydrogen octahydro-obacunoninate (II)

This compound was prepared according to the method of Dean and Geissman.[2] Methyl obacunoate[1] (0·5 g) was dissolved in acetic acid (20 ml) and shaken in an atmosphere of hydrogen in the presence of 1% palladium-on-alumina[11] (0·5 g). Absorption of 88·6 ml (3·6 moles) of hydrogen was observed (18 hr). The catalyst was filtered and the filtrate was evaporated under reduced press. The residue was dissolved in chloroform and shaken with bicarbonate solution. Acidification of the bicarbonate solution with dil HCl gave precipitates which were recrystallized twice from dil methanol as needles, m.p. 174–175° (dec) (164 mg). Infra-red spectrum (nujol): 2·87, 3·09, 3·6–4·0, 5·77, 5·83, 5·88 μ. (Found: C, 65·62; H, 8·67. Calc. for $C_{28}H_{42}O_8$: C, 65·56; H, 8·56%.)

Dimethyl octahydro-obacunoninate

Methyl hydrogen octahydro-obacunoninate dissolved in methanol was methylated with an excess of diazomethane in ether. The solvent was evaporated and the residue recrystallized twice from dil methanol as needles, m.p. 94–97°. Infra-red spectrum (nujol): 5·68, 5·83 μ. (Found: C, 61·84; H, 8·84. Calc. for $C_{28}H_{44}O_8 \cdot 2H_2O$: C, 61·74; H, 8·88%.) Dean and Geissman[2] reported that dimethyl octahydro-obacunoninate was obtained as a clear glass.

Catalytic reduction of the dilactone (V)

The dilactone (500 mg) dissolved in acetic acid (50 ml) was shaken in an atmosphere of hydrogen in the presence of 10% palladium-charcoal (250 mg). The mixture was shaken several times in air in order to activate the catalyst, in the course of the hydrogenation. Slow absorption of about 3 moles hydrogen ceased after 29 hr. The catalyst was filtered and the solvent evaporated under reduced press. The gummy residue was treated with a mixture of chloroform and aqueous bicarbonate solution.

The bicarbonate solution was acidified with dil HCl and the resulting precipitates filtered. Recrystallization from dil methanol gave VII as needles (220 mg), m.p. 132–133° (dec), which after being dried at 80°/1 mm sintered at 138° and melted at 140° with bubbling. This compound showed a pale blue color with acetic anhydride and sulphuric acid in chloroform. Negative reactions resulted with Ehrlich's and Brady's reagents. Infra-red spectrum (nujol): 2·87 (hydrate), 3·70–4·00 (carboxylic acid), 5·72 (γ-lactone; 5·69 μ in chloroform), 5·90 μ (carboxylic acid and ketone). (Found: C, 64·13; H, 8·10. Calc. for $C_{23}H_{34}O_7 \cdot H_2O$: C, 63·70; H, 8·10%.)

The acid (VII) was methylated with an ether solution of diazomethane. Recrystallization from methanol gave the methyl ester as needles, m.p. 199–202°. Infra-red spectrum (Nujol): 5·73 (5·69 μ in chloroform), 5·89 μ. (Found: C, 67·34; H, 8·20. Calc. for $C_{25}H_{38}O_7$: C, 66·94; H, 8·09%.)

The above chloroform solution was evaporated and recrystallization of the residue from dil methanol gave the tetrahydro-dilactone (VI) as needles (36 mg), m.p. 243–245° (dec). Infra-red spectrum (nujol): 5·68 (γ-lactone), 5·74 (δ-lactone), 5·84 μ (ketone). (Found: C, 65·98; H, 7·70. Calc. for $C_{24}H_{32}O_7$: C, 66·65; H, 7·46%.)

Desoxy-dilactone (IX)

A mixture of the dilactone (V, 0·5 g), freshly distilled hydriodic acid (0·6 g) and glacial acetic acid (30 ml) was heated at 80° for 4 hr. The reaction mixture was concentrated to a small volume (ca. 10 ml) and allowed to stand overnight after the addition of aqueous bisulphite solution. The separated precipitates were filtered, dried, dissolved in chloroform and chromatographed through a column containing silicagel (15 g). Elution with chloroform–acetone (9:1) yielded a crystalline mass which was crystallized from acetone–water as needles (175 mg), m.p. 306–307° (dec). On further recrystallizations from the same solvent the m.p. was raised to 339–340°. Infra-red spectrum (Nujol): 5·69 (γ-lactone), 5·88 μ (α,β-unsaturated δ-lactone and ketone). Ultra-violet spectrum: λ_{max}^{EtOH} 214 mμ

[10] T. V. Parke and W. W. Davis, *Analyt. Chem.* **26**, 642 (1954).
[11] A. C. Johnson, *Chem. Abstr.* **39**, 2001 (1945).

(ε 12,300); in difference curve with the absorption curve of the dilactone (V), λ_{max}^{EtOH} 218 mμ (ε 7,200). (Found: C, 69·98; H, 6·95. Calc for $C_{24}H_{28}O_6$: C, 69·88; H, 6·84%.)

Desoxylimonin (XI)*

A modification of the procedure of Geissman and Tulagin[6] was used for the preparation of desoxylimonin. Limonin (1·0 g) was heated at 60° in a mixture of acetic acid (15 ml) and hydriodic acid (15 ml) for 4 hr. The mixture was poured into water containing sodium bisulphite and extracted with chloroform. The chloroform layer was washed with water, bicarbonate solution and water, successively, dried and evaporated. Recrystallization of the residue from acetone–ethanol gave prisms, m.p. 332° (dec) (literature[6], m.p. 305° (dec)). Infra-red spectrum (Nujol): 5·75, 5·83 μ. Ultra-violet spectrum: λ_{max}^{EtOH} 215 mμ (ε 16,300); in difference curve with the absorption curve of limonin. λ_{max}^{EtOH} 218 mμ (ε 11,600). (Found: C, 68·84; H, 6·81. Calc. for $C_{26}H_{30}O_7$: C, 68·70; H, 6·65%.)

Dihydroetio-obacunone-dicarboxylic acid (XV)

(a) *From etio-obacunone-dicarboxylic acid* (XVI). Etio-obacunone-dicarboxylic acid[5] (0·5 g) dissolved in dioxane (30 ml) was shaken in atmosphere of hydrogen in the presence of 1% palladium-on-alumina[10] (0·5 g). Slow absorption of hydrogen ceased after 16 hr. The catalyst was filtered and the filtrate evaporated under reduced press. The residue was twice recrystallized from dioxane–water to give prisms (130 mg), m.p. 250–251° (dec). Infra-red spectrum (Nujol): 2·95 (hydroxyl), 5·73 (δ-lactone), 5·80 μ with a shoulder at 5·90 μ (carboxyls and ketone). Saponification equivalent: 153·7 (calc. for a dibasic acid: 150·6). (Found: C, 61·18; H, 7·39. Calc. for $C_{28}H_{32}O_9$: C, 61·05; H, 7·13%.)

(b) *From etio-obacunoic acid* (XII). Etio-obacunoic acid[5] (800 mg) dissolved in ethyl acetate (25 ml) was shaken in an atmosphere of hydrogen in the presence of 10% palladium-charcoal (200 mg). Absorption of 42·5 ml (0·93 mole) hydrogen was observed after about 2 hr. The catalyst was filtered and the filtrate evaporated under reduced press. Recrystallization of the residue from acetone–water gave the acid (XV) as prisms (473 mg), m.p. 237–238°, the m.p. was raised to 255° (dec) after several recrystallizations from the same solvent. The infra-red spectrum was identical with that of XV, obtained above.

(c) *From methyl dihydroetio-obacunoate* (XIV). Methyl dihydroetio-obacunoate[5] (178 mg) was heated on the water-bath in 0·1 N NaOH (25 ml) for 30 min. The mixture was evaporated to a small volume under reduced press and acidified (congo red) with dil HCl. The resulting crystals were collected and recrystallized from acetone–water to give prisms (0·13 g), m.p. 250–251° (dec), which were identified as XV by mixed m.p. and comparison of infra-red spectrum.

Dimethyl dihydroetio-obacunone-dicarboxylate (XVII)

Dihydroetio-obacunone-dicarboxylic acid (XV) was dissolved in dioxane and methylated with an excess of diazomethane in ether. The solvent was evaporated and the residue recrystallized from methanol to give prisms, m.p. 197–198°. (Practically quantitative yield.) Infra-red spectrum (Nujol): 2·88 (hydroxyl), 5·73 (δ-lactone and esters), 5·86 μ (ketone). (Found: C, 62·48; H, 7·63. Calc. for $C_{32}H_{36}O_9$: C, 62·48; H, 7·55%.)

Dimethyl anhydrodihydroetio-obacunone-dicarboxylate (XVIII)

(a) *With potassium hydrogen sulphate and acetic anhydride.* Dimethyl dihydroetio-obacunone-dicarboxylate (XVII, 1·10 g) and freshly fused potassium hydrogen sulphate (5 g) were refluxed in acetic anhydride (40 ml) for 15 min. The mixture was poured into ice-water and allowed to stand overnight. The resulting solid was filtered, dried, and recrystallized from methanol–water to give needles (0·9 g), m.p. 145–146° (sintered at about 80°). The m.p. was raised to 149–151° (sintered at about 90°) after recrystallization from the same solvent. Infra-red spectum (Nujol): 5·72 (δ-lactone and esters), 5·86 (ketone), 11·23 μ (terminal methylene). (Found: C, 64·75; H, 7·54. Calc. for $C_{32}H_{34}O_8$: C, 64·92; H, 7·41%.)

(b) *With phosphorous oxychloride and pyridine.* The dimethyl ester (XVII, 100 mg) dissolved in pyridine (4 ml) was mixed with freshly distilled phosphorous oxychloride (0·3 ml) under ice-cooling.

* The authors are indebted to Dr. T. Tokoroyama for these experiments.

The mixture was then heated on the water-bath for 45 min. After the mixture was evaporated to a small volume, it was poured into ice-water. After several hour's standing the resulting solid was filtered, dried, and recrystallized from methanol–water to give needles (80 mg), m.p. 146–148°, which were identical with the anhydro-compound (XVIII) obtained above.

Ozonization of dimethyl anhydrodihydroetio-obacunone-dicarboxylate (XVIII)

A solution of the anhydro-compound (4·3 g) in chloroform (60 ml) was ozonized with ozonized oxygen under ice-cooling (5 hr). The mixture was heated with 200 ml water on the water-bath for 1 hr. The aqueous layer was divided into two parts of equal volume. The one part was allowed to stand with dimedone (0·6 g) in water (200 ml) overnight, then heated on the water-bath for 1 hr. The mixture separated silky needles (0·35 g), m.p. 186–188°, pure and mixed with an authentic sample of formdimedone. The other part of the aqueous layer was mixed with 2,4-dinitrophenylhydrazine solution in dil HCl. Orange precipitates were filtered, dried and recrystallized twice from ethyl acetate–ethanol to give orange needles (0·22 g), m.p. 163–165°, pure and mixed with an authentic sample of 2,4-dinitrophenylhydrazone of formaldehyde.

The chloroform layer was dried and evaporated. The residue was recrystallized from chloroform–ether to give the norketone (XIX) as leaflets (3·00 g), bubbled at 107° after sintering at about 90°. This compound showed a positive iodoform reaction and a positive Beilstein reaction. Infra-red spectrum (Nujol): 5·73 (esters and δ-lactone), 5·83 (ketone), 5·86 (ketone), near 13·2 μ (chloroform). (Found: C, 56·19; H, 6·44; Cl, 8·78. Calc. for $C_{21}H_{32}O_8 \cdot \frac{1}{2}CHCl_3$: C, 56·13; H, 6·25; Cl, 10·15%.)

This compound, after being dried at 110°/1 mm for 6 hr, was recrystallized from methanol to give plates, m.p. 152–154° (sintered at about 80°), which showed a negative Beilstein reaction. Infra-red spectrum (Nujol): 5·73 (esters and δ-lactone), 5·85 μ (ketones). (Found: C, 60·19; H, 7·21. Calc. for $C_{24}H_{32}O_9 \cdot CH_3OH$: C, 60·47; H, 7·31%.)

Selenium dehydrogenation of the lithium aluminium hydride reduction product of methyl etio-obacunoate (XIII)

Methyl etio-obacunoate (2·5 g) dissolved in anhydrous tetrahydrofuran (60 ml) was added dropwise to the refluxed mixture of lithium aluminium hydride (2 g) and tetrahydrofuran (30 ml). Refluxing was continued more 3 hr and the excess of the hydride was decomposed by the careful addition of ethyl acetate. The mixture was decomposed by the addition of saturated sodium sulphate solution and filtered. The filter cake was washed with hot ethyl acetate. The filtrate and washings were combined, dried and evaporated under reduced press to viscous material (1·45 g), whose infra-red spectrum did not show any carbonyl bands.

The reduction product (1·6 g) was mixed with selenium (4 g) and heated at 280–300° for 14 hr, then 320–340° for 6 hr. The reaction mixture was powdered and extracted with ether. The ether extract was evaporated to a dark brown liquid (90 mg), which was dissolved in pet. ether (5 ml) and passed through a column containing alumina (5 g). Elution with pet. ether yielded a yellow liquid (43 mg) which was dissolved in ethanol (1 ml) and added to a hot solution of picric acid (70 mg) in ethanol (1 ml). Spontaneous evaporation separated orange red needles which were washed with methanol, filtered and recrystallized from methanol to give needles, m.p. 125–130°. The mixed m.p. with 1,2,5-trimethylnaphthalene, m.p. 135°, which was prepared from manool by selenium dehydrogenation, was not depressed.

Tetrahedron, 1961, Vol. 12, p. 277. Pergamon Press, Inc. Printed in Northern Ireland

BOOK REVIEW

J. A. DEAN: **Flame Photometry.** McGraw-Hill, New York, Toronto, London, 1960. viii + 354 pp.

FLAME PHOTOMETRY has become more and more widely used over the last fifteen years. Despite this there was no adequate textbook on the subject in English until the appearance of this excellent book. The author divides the subject into theoretical principles, instrumentation and technique, flame photometry applied to the individual elements, and applications.

The book is clearly and interestingly written, and unlike some other available texts contains an adequate discussion of the basic principles of the method.

The author succeeds in introducing some order into the many conflicting reports in the literature, and this book is essential reading for anyone who wishes to use flame photometric methods intelligently. It can be most heartily recommended, and most analysts will want to have it on their shelves.

I. MACINTYRE

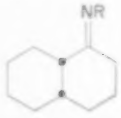
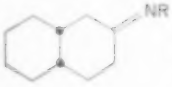
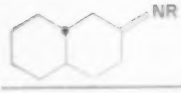
Tetrahedron, 1961, Vol. 12, p. 278. Pergamon Press, Inc. Printed in Northern Ireland

ERRATUM

J. W. POWELL and M. C. WHITING: The decomposition of sulphonylhydrazone salts: mechanism and stereochemistry—II. The pyrolysis of the diazodecalins, *Tetrahedron* **12**, 168–172 (1961).

The formulae along the top line of Table 1, on p. 169 of the above article, were incorrectly printed upside down. The table should read:

TABLE 1. PRODUCTS OF THE ALKALINE DECOMPOSITION OF THE DECALONE METHANESULPHONYLHYDRAZONES

Decalone Methane-sulphonyl-hydrazone	Reagent					
	A G	25% 27%	75% 73%			
	A G		51% 48%	49% 52%		
	A G	74% 82%			26% 18%	
	A G				35% 45%	65% 55%

=NR is $=N.NH.SO_2.CH_3$, giving $=N^+=N^-$
Reagent A: 1·3 N solution of sodium in acetamide, at 156°.
Reagent G: 1·3 N solution of sodium in ethylene glycol, at 156°.

Tetrahedron, 1961, Vol. 12, p. 279. Pergamon Press, Inc. Printed in Northern Ireland

VOL. 12 1961

Papers to be published in a forthcoming issue*

Proceedings of a Conference on Rotatory Dispersion: Related Theory and Application

WERNER KUHN: Rotary dispersion and the vibrating momentum of optically active absorption bands.

CARL DJERASSI: Application of anomalous optical rotary dispersion to organic chemical problems.

W. KLYNE: Optical rotary dispersion. Some applications to structural and stereochemical problems in organic chemistry.

ALBERT MOSCOWITZ: Some applications of the Kronig–Kramers theorem to optical activity.

W. KAUZMANN, F. B. CLOUGH and I. TOBIAS: The principle of pairwise interactions as a basis for an empirical theory of optical rotary power.

JAMES H. BREWSTER: Some applications of the conformational dissymmetry rule.

ELKAN R. BLOUT: Helical sense of polypeptides and proteins.

IGNACIO TINOCO, JR., ROBERT W. WOODY and KIWAMU YAMAOKA: Optical rotation and polypeptide structure.

JEN TSI YANG: Optical rotatory dispersion of polypeptides and proteins.

B. JIRGENSONS: Optical rotatory dispersion of globular proteins.

JOZSEF STREM, Y. S. R. KRISHNA-PRASAD and JOHN A. SCHELLMAN: The rotatory dispersion of amino acids.

JACQUES R. FRESCO: Optical rotatory properties of polynucleotides and nucleic acids.

PAUL O. P. TS'O and GEORGE HELMKAMP: Studies on the secondary structure of nucleic acids by means of optical rotation.

GUNTHER L. EICHHORN: Rotatory dispersion studies of biologically active metalloporphyrin compounds.

CONMAR ROBINSON: Liquid-crystalline structure in polypeptide solutions.

LEON L. JONES and HENRY EYRING: A many electron model for optical rotation.

* Vol. 13, Nos. 1-3.